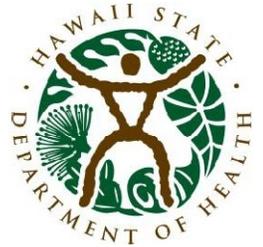




State of Hawaii
Department of Health
4348 Waialea Avenue #648
Honolulu, HI 96816



Medical Cannabis Registry

PETITION TO ADD A DEBILITATING MEDICAL CONDITION IN 2020

Instructions

1. ALL items on the form MUST be completed.
2. Petitions and any supporting documents may be submitted as follows:
 - a. Email to: medicalmarijuana@doh.hawaii.gov before the close of business (4:30PM) on **Thursday, April 30, 2020**. Please use the subject line: Petition to Add New Condition. Note that the DOH will not make public any information that is protected pursuant to Chapter 92F, HRS, the Uniform Information Practices Act.
 - b. Postal mail to: 4348 Waialea Avenue, #648, Honolulu, Hawaii 96816. Mailed petitions must be received by **Thursday, April 30, 2020**.
 - c. Hand delivered to: Kinau Hale at 1250 Punchbowl Street, Honolulu, Hawaii 96813 before the close of business (4:30PM) on **Thursday, April 30, 2020**. Hand delivered petitions must be left with the security guard and addressed to the Medical Cannabis Registry Program **ATTN: Petition to Add New Condition**.
3. For best results, complete and thorough petitions that include substantiated and reputable research have the best chance of succeeding. DOH recommends that you do the following for items #2- #8 on the petition form:
 - a. Please cite research, published evidence, or findings using the standard American Medical Association (AMA) format for each piece of research, published evidence, or findings that you reference in your submittal or at a minimum the following:
Author's Name; Title of Article; Name of Publication; Date of Publication; Volume/Section/Chapter/Page/Line as applicable; and URL (if applicable).
 - b. Please attach a PDF copy of the cited material to your submittal. These documents will NOT be returned.
 - c. Please be sure to indicate the specific section, page(s), lines, etc., of the attachment that you want reviewed/considered as evidence.
4. To view a list of current conditions click here: [Current Debilitating Medical Conditions](#)

Petitioner

Name

I am a Physician/APRN
 Potentially qualifying patient (a person who has been diagnosed with the medical condition for which the petition is being made)

Street Address

City

State

Email

I prefer the following and give my consent for all notifications about my petition to be by:

- Mailing address
 Email address
 Both mailing and email addresses

If I have indicated communication via email, and if for any reason email communication is not successful (i.e. email provided bounces or is kicked back to DOH), then I further understand that communication will be by regular U.S. postal service to the mailing address that I have provided. I also take full responsibility for any inaccurate email or U.S. postal mail address provided.

Petitioner Content

(1) State the specific medical condition or its treatment for which the petition is being made.

Insomnia

(2) State the reason(s) why the medical condition or its treatment should be added to the list of qualifying debilitating medical conditions for which medical cannabis may be used. For best results, please cite research, published evidence, or scientific findings AND attach a PDF copy to your submittal. Indicate specific lines, page, section. Please use standard AMA format as outlined in the instructions.

Insomnia is a widespread, serious and debilitating condition, to which the current traditional treatments are dangerous (alcohol, ambien) or have a low success rate (relaxation, exercise, glass of milk). Patients with other qualifying conditions report that cannabis helps with insomnia. As cannabis is non toxic and highly effective for insomnia, insomnia should be added to the list of qualifying conditions for those people who do not currently have a qualifying condition.

(REF #65) <https://www.ncbi.nlm.nih.gov/books/NBK19961/>

Institute of Medicine (US) Committee on Sleep Medicine and Research; Colten HR, Altevogt BM, editors.

Washington (DC): [National Academies Press \(US\)](#); 2006.

It is estimated that 50 to 70 million Americans chronically suffer from a disorder of sleep and wakefulness, hindering daily functioning and adversely affecting health and longevity. There are around 90 distinct sleep disorders; most are marked by one of these symptoms: excessive daytime sleepiness, difficulty initiating or maintaining sleep, and abnormal events occurring during sleep. The cumulative long-term effects of sleep loss and sleep disorders have been associated with a wide range of deleterious health consequences including an increased risk of hypertension, diabetes, obesity, depression, heart attack, and stroke. **After decades of research, the case can be confidently made that sleep loss and sleep disorders have profound and widespread effects on human health.**

(REF #99) The National Academy of Sciences Institute of Medicine, in its 1999 report on marijuana, found that many serious and debilitating conditions had the symptom of insomnia and that medical marijuana was able to safely treat insomnia by inducing sleep.

Page 83 of the pdf:

The most commonly reported effects of smoked marijuana are a sense of well-being or euphoria and increased talkativeness and laughter alternating with periods of introspective dreaminess followed by lethargy and **sleepiness** (see reviews by Adams and Martin, 1996,¹ Hall and Solowij,⁵⁹ and Hall et al. ⁶⁰).

Page 164:

Victims of spinal cord injury reporting at IOM workshops noted that smoking marijuana reduces their muscle spasms, their nausea, and **the frequency of their sleepless nights.**

(REF #40) The National Academies of Sciences, Engineering, and Medicine reviewed all marijuana research conducted and published from 1999-2016 and published a comprehensive report on cannabis and health.

National Academies of Sciences, Engineering, and Medicine 2017. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC: The National Academies Press.

<https://doi.org/10.17226/24625>

<https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state>

Page 13:

There is moderate evidence that cannabis or cannabinoids are effective for:

Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols) (4-19)

A safety profile of Medical Marijuana can be found in the first year report of the Minnesota medical marijuana program. The Minnesota Department of Health surveyed 1500+ medical marijuana patients enrolled in the program.

(REF #11) <https://www.health.state.mn.us/people/cannabis/about/firstyearreport.html>

Adverse Side Effects: At this point, the safety profile of the medical cannabis products available through the Minnesota program seems quite favorable. Approximately 20-25% of enrolled patients report negative physical or mental side effects of some kind, with the majority – around 60% - reporting only one and 90% reporting three or fewer. The vast majority of adverse side effects, around 90%, are mild to moderate in severity. An assessment of the 30 patients reporting severe side effects, meaning “interrupts usual daily activities,” found no apparent pattern of patient age, medical condition, or type of medical cannabis used. The most common adverse side effects are dry mouth, drowsiness, and fatigue. Fortunately, up to the present no serious adverse events (life threatening or requiring hospitalization) have been reported.

Medical Marijuana's mild to moderate side effects of dry mouth, drowsiness and fatigue are easily tolerated by the vast majority of patients. Fatigue means being tired, and is the desired effect for people who suffer from insomnia and wish to feel tired so they can sleep.

(REF #77) <https://www.mass.gov/files/documents/2019/07/09/MBHS-full-report-final.pdf>

<https://www.mass.gov/report/massachusetts-department-of-public-health-marijuana-research>

The Marijuana Baseline Health Study (MBHS)

A legislative mandate required the Massachusetts [Department of Public Health \(DPH\)](#) to conduct a baseline study to investigate marijuana use in Massachusetts. The report published confirms the consensus that marijuana use improves sleep and treats insomnia for a large percentage of people.

Page 148:

Results from this survey suggest that respondents appear to be treating a wide range of medical conditions, and often more than one at a time. **The top 5 medical conditions being treated were** anxiety (60% or all respondents), chronic pain (46%), **insomnia (43%)**, depression (42%), and stress (41%), and the average number of conditions being treated by medical marijuana is 4.7.

The CDC says "Insufficient Sleep Is a Public Health Problem". <https://www.cdc.gov/features/dssleep/index.html>

The National Department of Transportation estimates drowsy driving to be responsible for 1,550 fatalities and 40,000 nonfatal injuries annually in the United States.

https://one.nhtsa.gov/people/injury/drowsy_driving1/Drowsy.html

A lack of sleep among the U.S. workforce is costing approximately \$411 billion and losing 1.2 million working days per year, a new study has found.

<http://fortune.com/2016/11/30/sleep-productivity-rand-corp-411-billion/>

The most widely prescribed medication for insomnia is Ambien, which can cause its users to sleep walk, sleep drive, sleep eat and other actions while unconscious.

http://www.huffingtonpost.com/2014/01/15/ambien-side-effect-sleepwalking-sleep-aid_n_4589743.html

Ambien, a drug that can make people sleepwalk and get into cars and drive - causing numerous accidents and deaths, is Schedule 4. Marijuana is Schedule 1. Ambien was first discovered in the early 1980s and used for insomnia in France in 1988, USA in 1992.

<http://www.emedexpert.com/facts/zolpidem-facts.shtml>

The choice for relief of insomnia is between an FDA approved "BLACK BOX" drug that is 30 years old and still has unknown side effects, or medical marijuana which has been used safely and effectively by humans for thousands of years by every country inhabited by humans on the entire planet.

Comparing medical marijuana to other insomnia medications shows that medical marijuana has less side effects, no toxicity and is safer.

Benadryl is another FDA approved treatment commonly used to treat Insomnia:

Overall driving performance was the poorest after taking diphenhydramine, and participants were most drowsy after taking diphenhydramine (before and after testing). *The authors concluded that diphenhydramine clearly impairs driving performance, and may have an even greater impact than does alcohol on the complex task of operating a motor vehicle.*

<https://one.nhtsa.gov/people/injury/research/job185drugs/diphenhydramine.htm>

While the study of marijuana and driving is clear: <http://blog.caranddriver.com/marijuana-doesnt-pose-significant-risk-in-car-crashes-nhtsa-says/>

<https://one.nhtsa.gov/people/injury/research/job185drugs/cannabis.htm>

Which reports on a study by NHTSA:

When factoring age, sex, and race, there was no "significant increased risk of crash involvement" due to marijuana use.

http://www.nhtsa.gov/staticfiles/nti/pdf/812117-Drug_and_Alcohol_Crash_Risk.pdf

A general consensus has developed from population-based studies that approximately 30% of a variety of adult samples drawn from different countries report one or more of the symptoms of insomnia.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1978319/>

(REF #8) In 1889, Dr Ed Birch published case reports of patients and documented that cannabis was a “well known remedy for insomnia” in the Lancet journal.

I prescribed the cannabis simply with a view to utilising a well-known remedy for insomnia, but it did much more than procure sleep.

As evidenced by the included medical marijuana patient surveys in other states and countries, adults are using medical marijuana to treat this disease. Patients will continue to use medical marijuana to treat symptoms whether or not you approve this condition. Approving this condition to the list of Qualifying Conditions in the Hawaii Medical Cannabis Program has the only effect of protecting sick people from arrest or penalty. These patients are currently breaking the law by using a safe and non-toxic plant that they can grow themselves. The alternative are prescriptions that cost thousands of dollars per month, that the FDA approves even if it is toxic and poisons and kills many Americans each year.

(3) Describe the **extent to which** the medical condition is generally accepted by the medical community as a valid, existing medical condition. For best results, please cite research, published evidence, or scientific findings AND attach a PDF copy to your submittal. Indicate specific lines, page, section. Please use standard AMA format as outlined in the instructions.

Insomnia is a common and serious debilitating medical condition, accepted by the medical community, affecting millions in the US each year. Veterans suffer from debilitating insomnia in percentages more than the general population.

(REF #68) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5930488/>

Insomnia in Military Veterans

Chronic Insomnia Disorder is a common behavioral sleep disorder clinically defined as dissatisfaction with sleep quantity or quality marked by complaints of difficulty falling or staying asleep, waking up earlier than desired, or sleep that is non-restorative and the cause of significant daytime impairment. Such problems are not related to other medical or sleep disorders, exist despite adequate opportunity and environment for sleep, and are endorsed three or more nights per week for three months or longer ([American Psychiatric Association, 2013](#)). Insomnia and/or insomnia-like symptoms are present in 27–54% of military personnel and veterans ([Hoge, W. et al., 2008](#); [Mysliwiec, McGraw, Smith, Trapp, & Roth, 2013](#)), rates that are two to three times higher than in the general U.S. adult population ([Ford, Cunningham, Giles, & Croft, 2015](#); [Roth, 2007](#)). The rate of incident insomnia cases in military personnel saw a 19-fold increase from 2000 to 2009 ([Mysliwiec et al., 2013](#)). The prevalence of insomnia among Veterans Health Administration (VHA) users is expected to continue to rise as many troops who served after September 11, 2001 continue to retire from military service and begin accessing VHA healthcare in the coming years ([Campbell, Shattuck, Germain, & Mysliwiec, 2015](#)).

Consequences of Insomnia

Persistent insomnia can lead to poor health outcomes and chronic conditions ([Fernandez-Mendoza & Vgontzas, 2013](#); [Taylor et al., 2007](#)), exacerbate symptoms of traumatic brain injury ([Macera, Aralis, Rauch, & MacGregor, 2013](#)), reduce overall quality-of-life ([Katz & McHorney, 2002](#)), and increase risk for morbidity and premature mortality ([Dew et al., 2003](#); [Kripke, Garfinkel, Wingard, Klauber, & Marler, 2002](#)). Chronic sleep problems can also negatively impact day-to-day outcomes including task performance ([Pilcher & Huffcutt, 1996](#)), stress coping ([Hamilton, Delwyn, & Karlson, 2007](#)), and management of chronic health conditions ([Ahn, Jiang, Smith, & Ory, 2014](#)).

Function, Performance and Health Management

Chronic insomnia impairs function and performance across cognitive, emotional, social, and physical domains ([Killgore, Balkin, & Westensten, 2006](#); [Killgore et al., 2008](#); [Pilcher & Huffcutt, 1996](#)). Adequate functioning in these areas enables veterans to adapt to and cope with daily hassles and reintegration stressors noted earlier. However, impairments in one or more domains can reduce ability to cope with acute and ongoing stressors. As a result, functional performance and independence decline, thereby decreasing the likelihood of successful reintegration into civilian life ([Institute of Medicine, 2013](#); [Pilcher & Huffcutt, 1996](#)).

Many of these aforementioned impairments can also reduce a veteran's capacity to cope with health-related stressors, a concept of particular interest to clinicians and health services researchers within the VHA. Medically complex patients, defined as individuals with two or more chronic conditions, who are challenged by managing such conditions ([Shippee, Shah, May, Mair, & Montori, 2012](#)), represent a growing subgroup of veterans utilizing VHA healthcare ([Yoon, Schott, Phibbs, & Wagner, 2011](#); [Yu et al., 2003](#)). Medical complexity is often marked by a cycle of ongoing acute and chronic health-related stressors. Patients cycle through these stressors and strive to achieve and maintain a balance between workload demands (i.e. management of chronic diseases) and physical and psychological resources ([Zullig et al., 2016](#)). Successful balance and management of stressors is bolstered by high physical and psychological reserve and capacity ([Zullig et al., 2016](#)). These new models of complexity support the idea that capacity is malleable and can be impacted by resources, behaviors, and events on individual and community levels. Although sleep problems, including insomnia, are gaining more attention within the VHA, sleep patterns and behaviors are not explicitly addressed in these models.

Mental Health

Insomnia symptoms are common among veterans with mental health disorders. In one study, more than three-quarters reported difficulty falling or staying asleep and just over one-half reported being at least moderately distressed about sleep that was restless or disturbed ([Ulmer et al., 2015](#)). Although this research sample was designed to over-recruit veterans with mental health symptoms, this same study drew attention to the notably high prevalence of sleep difficulties in veterans without a mental health diagnosis, including approximately seventy percent who met clinical criteria for poor sleep quality, defined as a score of five or greater on the Pittsburgh Sleep Quality Index ([Buysse, Reynolds, Monk, Berman, & Kupfer, 1989](#)).

The high rate of sleep problems among veterans without mental health diagnoses is alarming given that research with veteran and non-veteran populations has found that chronic sleep problems predict incident mental health diagnoses ([Baglioni et al., 2011](#); [Breslau, Roth, Rosenthal, & Andreski, 1996](#); [D. Ford & Kamerow, 1989](#); [Perlis et al., 2006](#)) and suicidal ideation ([Pigeon, Britton, Ilgen, Chapman, & Conner, 2013](#); [Pigeon, Piquart, & Connor, 2012](#)) as well as persistence of existing mental health problems, including depression ([Pigeon, Unutzer, & Perlis, 2008](#)), and increased risk for readmission to a partial hospitalization psychiatry program ([Koffel, Thuras, Chakravorty, Germain, & Khawakaja, 2015](#)). In a large study of OEF/OIF service members, researchers found that military personnel with predeployment insomnia symptoms had greater odds of developing depression, anxiety, and PTSD at follow-up ([Gehrman et al., 2013](#)). Another longitudinal study found that insomnia measured at four months post-deployment was a significant predictor of depression and PTSD at 12-months post-deployment ([Wright et al., 2011](#)).

<https://medlineplus.gov/insomnia.html>

What other problems can insomnia cause?

Insomnia can cause daytime sleepiness and a lack of energy. It also can make you feel anxious, depressed, or irritable. You may have trouble focusing on tasks, paying attention, learning, and remembering. Insomnia also can cause other serious problems. For example, it could make you may feel drowsy while driving. This could cause you get into a car accident.

(4) Describe the symptoms and other physiological or psychological effects experienced by an individual suffering from the medical condition or its treatment and **the extent to which** these symptoms and physiological or psychological effects are debilitating. Note: "Debilitating" generally means impairing the ability of a person to accomplish activities of daily living. For best results, please cite research, published evidence, or scientific findings AND attach a PDF copy to your submittal. Indicate specific lines, page, section. Please use standard AMA format as outlined in the instructions.

(REF #65) <https://www.ncbi.nlm.nih.gov/books/NBK19961/>

Institute of Medicine (US) Committee on Sleep Medicine and Research; Colten HR, Altevogt BM, editors.

Washington (DC): [National Academies Press \(US\)](#); 2006.

It is estimated that 50 to 70 million Americans chronically suffer from a disorder of sleep and wakefulness, hindering daily functioning and adversely affecting health and longevity. There are around 90 distinct sleep disorders; most are marked by one of these symptoms: excessive daytime sleepiness, difficulty initiating or maintaining sleep, and abnormal events occurring during sleep. **The cumulative long-term effects of sleep loss and sleep disorders have been associated with a wide range of deleterious health consequences including an increased risk of hypertension, diabetes, obesity, depression, heart attack, and stroke. After decades of research, the case can be confidently made that sleep loss and sleep disorders have profound and widespread effects on human health.**

(REF #66) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1978319/>

Roth T. (2007). Insomnia: definition, prevalence, etiology, and consequences. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*, 3(5 Suppl), S7–S10.

Due to its chronicity, insomnia is associated with substantial impairments in an individual's quality of life. In several studies, insomniacs reported decreased quality of life on virtually all dimensions of the 36-item Short Form Health Survey of the Medical Outcomes Study (SF-36), which assesses 8 domains: (1) physical functioning; (2) role limitation due to physical health problems (role physical); (3) bodily pain; (4) general health perceptions; (5) vitality; (6) social functioning; (7) role limitations due to emotional health problems (role emotional); and (8) mental health.^{16–18} One study compared SF-36 results in groups of mild and severe insomnia patients with groups of patients diagnosed with depression or congestive heart failure (CHF).¹⁹ Severe insomnia patients had numerically greater loss of function than patients with CHF in reported pain, emotional effects, and mental health effects. Additionally, insomnia patients also reported more physical problems than patients with depression.¹⁹

Research has shown that among the daytime consequences of insomnia, the increased occurrence of accidents poses the greatest health risk. Insomniacs are 2.5 to 4.5 times more likely than controls to have an accident.^{20,21} In a sample of 8,625 community respondents in France, Léger et al. reported that 8% of insomniacs and 1% of non-insomniacs had an industrial accident in the past 12 months.²² Work productivity is also compromised among insomniacs due to work-related problems (ie, higher rates of absenteeism, decreased concentration, and difficulty performing duties). Kuppermann and colleagues²³ found that individuals reporting a current sleep problem were more likely than good sleepers to have decreased job performance and to have been absent from work in the last month due to health problems. Simon and VonKorff²⁴ evaluated insomnia in a staff-model health maintenance organization population (N=1,962). After adjusting for age, gender, and chronic disease, days of restricted activity due to illness and days spent in bed were about twice as common among insomniacs compared with non-insomniacs. Additionally, mean total health care expenditures were 60% higher in the insomnia group relative to the controls.

Population- and clinic-based studies have demonstrated a high rate of psychiatric comorbidities in patients with chronic insomnia. In fact, insomnia is more frequently associated with psychiatric disorders than any other medical illness.²⁵ For example, in the Epidemiologic Catchment Area study, 40% of insomniacs had a comorbid psychiatric disorder compared with 16.4% of those with

no sleep complaints.⁸ Additionally, depression and anxiety are the most common comorbid psychiatric disorders in insomniacs. It has traditionally been assumed that insomnia is secondary to the psychiatric disorder; however, given the chronicity of insomnia, it is possible that in some, if not most, cases the insomnia precedes the psychiatric disorder. In fact, it is possible that insomnia represents a significant risk for the development of a subsequent psychiatric disorder. In a large-scale European population-based study (N=14,915), it was found that insomnia more often preceded rather than followed incident cases of a mood disorder.²⁶ This effect is even more pronounced for relapses of the mood disorder, where in 56.2% of cases, insomnia symptoms preceded symptoms of a mood disorder relapse. In contrast, in chronic insomnia patients with a comorbid anxiety disorder, the first occurrence of anxiety or a relapse preceded insomnia in most instances.

To further understand the relation of sleep and psychiatric disorders, several longitudinal studies have examined the evolution of psychiatric disorders among insomnia patients. These studies used follow-up periods ranging from 1 to 40 years, with the majority using a 1- to 3-year follow-up period. In all of these studies, insomnia has been found to confer a substantial risk for the development of a depressive disorder.^{27,28} Typically, the relative risk was approximately 5 (range 2–40), and in all cases it was statistically significant. While some studies also reported an increased risk for anxiety or drug abuse, neither of these was consistently found. Finally, longitudinal studies in subjects with affective disorders show that depressed patients who experience improvements in sleep will also experience a more rapid antidepressant response; while those patients whose insomnia persists will have a short time to relapse.^{29,30} What is clearly needed are clinical trials to assess the impact of insomnia therapy on incidence of depression as well as the time to relapse in depressed patients who are in remission.

The question then arises as to whether insomnia causes depression, vice versa, or both. The close association of insomnia with depression is likely related to common underlying pathophysiological mechanisms for sleep and mood regulation that make the individual vulnerable to both conditions. Data have shown that both the diagnosis of insomnia and the severity of the sleep disturbance are related to overactivation of the hypothalamic-pituitary-adrenal (HPA) axis and the hypersecretion of cortisol.³¹ Recent evidence suggests that there may be some neuroendocrine and clinical similarities between insomnia and depression. Corticotropin-releasing factor (CRF) dysregulation has been implicated in the pathogenesis of psychiatric disorders such as depression³² as well as in the mediation of hyperarousal seen in primary insomnia.³³ This abnormality might represent the common risk factor, and therefore, it is quite possible that both disorders would respond to the same therapeutic intervention (eg, corticotropin-releasing hormone antagonists).

(5) If one or more treatments for the medical condition, rather than the condition itself, are alleged to be the cause of a person's suffering, describe **the extent to which the treatments causing suffering are generally accepted by the medical community as valid treatments for the medical condition.** For best results, please cite research, published evidence, or scientific findings AND attach a PDF copy to your submittal. Indicate specific lines, page, section. Please use standard AMA format as outlined in the instructions.

This petition is for the medical condition of insomnia, not the treatment of insomnia.

The prescription medication treatment of insomnia causes zombie like side effects when awake, and sleepwalking effects when asleep.

(REF #69) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4689974/>

Residual medication effects—such as feelings of being drowsy, groggy, or sluggish the next day, difficulty concentrating/remembering, or sleeping too much—were reported by approximately four out of every five individuals currently using prescription sleep medication. Overall, findings showed significant burden experienced by patients reporting residual sleep medication effects relative to those not reporting such effects.

Though patients with and without perceived residual effects suffered a similar number of nights with sleep problems (falling

asleep, staying asleep, waking before the alarm, or any problem), the experience of residual effects was associated with an average of one more day per week of “unrestful sleep.” One potential explanation is that the residual effects of the sleep medication itself are responsible for the difference, though this is only speculation; the present analysis was not designed to identify the cause. Patients reporting residual effects were also less satisfied with their medications. Moreover, there were clear relationships between increasingly severe residual symptoms and decreased satisfaction, as well as increasingly severe residual symptoms and greater work and activity impairment, and greater sleep-related interference in home management, ability to work, and social relationships. Though respondents reporting residual effects indicated they experienced more psychiatric symptomatology and other comorbidities than those not experiencing such effects, the relationships between functioning and residual symptom severity remained significant after these and other relevant covariates were accounted for.

...

Ultimately, patients who experience residual sleep medication effects represent a group with significant impairment of workplace, home, and social life activities; as the perceived severity of the residual symptoms increases, so does the burden. Thus, thorough medical and psychosocial/behavioral assessment of individuals experiencing residual effects is recommended (especially for the elderly). Also, improved management of insomnia would be beneficial. Behavioral and cognitive interventions have essentially no side effects and have been shown to lead to long-lasting, sustained improvements in sleep symptoms and parameters over 6 months to 24 months [28]. However, the degree of sleep medication use in this sample demonstrates that many may prefer, or need, pharmacotherapy for insomnia, highlighting a need for medications with fewer residual symptoms. The development of sleep medications with reduced residual effect profiles will be important for treatment of this patient population.

(REF #69)

Of the hypnotics, benzodiazepines and non benzodiazepine hypnotics with longer half-lives tend to produce residual impairment or “hang over,” particularly with middle-of-the-night dosing and regular use [17, 18]. Residual effects of hypnotics include sedation, cognitive impairment, motor incoordination, ataxia, dizziness, and gastrointestinal upset. In the elderly, the use of sedating drugs is dangerously associated with increased fall risk [19].

Meanwhile, the use of some antidepressants to treat insomnia has been associated with increased suicidal ideation, increased mania / hypomania in patients with bipolar disorder, and exacerbation of restless legs syndrome [20]. Further, the use of anticonvulsants (e.g., pregabalin) can produce daytime sedation, dizziness, and cognitive impairment [13]. Finally, the use of antipsychotics has been correlated with exacerbation of restless legs syndrome and increased mortality, particularly in elderly individuals [11]. From the standpoint of concern for public safety, insomnia treatments have been shown to impair next-day driving and increase the risk of motor vehicle accidents, particularly in women [21].

Ambien and other sleep medications have side effects of amnesia, sleep walking, sleep driving, sleep eating, sleep sex, and other activities done while unconscious. This pharmaceutical treatment is generally accepted by the medical community as a treatment for insomnia.

(REF #67) <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2762721/>

<https://abcnews.go.com/Health/MindMoodNews/story?id=8160299&page=1>

<https://www.nbcnews.com/health/health-news/sleeping-pills-raise-car-crash-risk-study-finds-n373891>

<https://www.today.com/health/while-i-was-sleeping-shopping-sprees-sugar-binges-other-confessions-1D80287242>

(6) Describe the availability of conventional medical therapies other than those that cause suffering to alleviate symptoms caused by the medical condition or its treatment. For best results, please cite research, published evidence, or scientific findings AND attach a PDF copy to your submittal. Indicate specific lines, page, section. Please use standard AMA format as outlined in the instructions.

Treatments include lifestyle changes, counseling, and medicines:

- Lifestyle changes, including [good sleep habits](#), often help relieve acute (short-term) insomnia. These changes might make it easier for you to fall asleep and stay asleep.
- A type of counseling called cognitive-behavioral therapy (CBT) can help relieve the anxiety linked to chronic (ongoing) insomnia
- Several medicines also can help relieve your insomnia and allow you to re-establish a regular sleep schedule

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2924526/>

First line pharmacotherapy

These drugs carry the highest level of evidence supporting efficacy and safety.

Benzodiazepines

Benzodiazepines are frequently prescribed to treat insomnia. These hypnotics reduce latency to sleep onset and total awakenings by increasing total sleep duration. Benzodiazepines enhance the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) by increasing the affinity of GABA for its receptor. Benzodiazepines non-selectively bind to an allosteric site and affect the GABA-A receptor complex to allow a greater number of chloride ions to enter the cell when GABA interacts with the receptor and therefore enhance the inhibitory action of GABA. This accounts for their sedative, anxiolytic, myorelaxant, and anticonvulsant properties. Five benzodiazepines (estazolam, flurazepam, quazepam, temazepam, and triazolam) have an FDA-approved indication for the management of insomnia. Dose, distinguishing pharmacokinetic properties (absorption rate, distribution, and elimination half-life), and risk-benefit ratio should be considered when selecting the most appropriate medication. The lowest effective dose should be used to minimize side effects, and long-acting benzodiazepines with active metabolites should be avoided in the elderly.

Major side effects of short-acting benzodiazepines include rebound insomnia and anterograde amnesia. Intermediate- and longer-acting benzodiazepines are less effective for inducing sleep, but are indicated for sleep maintenance and decreasing nocturnal awakenings.^[44] Long-acting medications are best indicated for people with insomnia as well as concomitant daytime anxiety. Accumulation of active metabolites is problematic in elderly patients and in those patients with impaired liver function as it can cause confusion and cognitive dysfunction. Benzodiazepines are contraindicated in patients with acute alcohol intoxication with depressed vital signs, a history of substance abuse, and during pregnancy.

Benzodiazepines should be used cautiously in patients with chronic pulmonary insufficiency or untreated sleep apnea. They are frequently used in mood disorders but a worsening of the dysphoric symptoms and precipitation of suicide has been noted in depression, while hypomania or frank mania and paradoxical hyper-excited states can also occur.^[42] However, long-term use (beyond 4 weeks) is associated with dependence, discontinuation syndrome, difficulty in new learning abilities, and blunting of emotions.^[45]

Non-benzodiazepine hypnotics

Non-benzodiazepine hypnotics include zopiclone, zolpidem, and zaleplon.

Zopiclone

Zopiclone is a non-benzodiazepine hypnotic of the cyclopyrrolone class. It is effective for reducing sleep latency and nocturnal awakenings and increasing total sleep time. Zopiclone delays the onset of rapid eye movement (REM) sleep but does not reduce consistently the total duration of (REM) periods. Rebound effects have been reported but are minimal. The incidence of adverse effects is low at recommended doses (3.75–7.5 mg).^[46]

Zolpidem

Zolpidem is a non-benzodiazepine hypnotic of the imidazopyridine class. It exhibits hypnotic effects with minimal myorelaxant, anticonvulsant, and anxiolytic properties, as it preferentially binds with the GABA-A receptor complexes with an alpha-1 subtype. Zolpidem is effective for reducing sleep latency and nocturnal awakenings and increasing total sleep time. Rebound effects are minimal. Common side effects include drowsiness, dizziness, and headache.[\[47\]](#)

Zaleplon

Zaleplon, like zolpidem, belongs to the imidazopyridine class of non-benzodiazepine hypnotics. The pharmacology of these two drugs is similar; however, zaleplon has an ultra-brief duration of effect.[\[48\]](#) It is effective for reducing time to sleep onset, but is not as effective for reducing nighttime awakenings or increasing total sleep time. No next-day sedation or rebound insomnia is documented with zaleplon at recommended doses (5–10 mg).

Eszopiclone

Eszopiclone, which is the active stereoisomer of zopiclone, acts as an agonist at benzodiazepine (BNZ) receptors. Well absorbed orally, about 3 mg of eszopiclone is equivalent to 10 mg of diazepam.[\[49\]](#) Although FDA approved for the management of chronic insomnia, there have been several reports of adverse effects like headaches, day-time drowsiness, loss of coordination, GI effects, decreased sexual desire, painful menstruation, and breast enlargement in males, leading a major reviewer to comment that the risk-benefit ratio should be weighed carefully due to the possible adverse effects such as cancer, infection, and death.[\[50\]](#)

Ramelteon

A melatonin agonist, it acts by selectively binding to the melatonin receptors (MT1, MT2) in the suprachiasmatic nucleus (SCN). It has also recently been approved for the treatment of insomnia and is the only non-scheduled prescription drug available in the United States for the treatment of insomnia. It has been shown to be effective in the elderly.[\[51\]](#)

No specific agent within this group is recommended as preferable to the others in a general sense; each has been shown to have positive effects on sleep latency, total sleep time (TST), and/or wake after sleep onset (WASO) in placebo-controlled trials.[\[52-55\]](#)

Second line pharmacotherapy

These drugs have moderate level of evidence supporting their efficacy and tolerability.

Antidepressants

Tricyclic antidepressants (TCAs) such as amitriptyline, doxepin, and nortriptyline are effective for inducing sleep and improving sleep continuity.[\[56\]](#) These agents should be used at their lowest effective dose to minimize anticholinergic effects and to minimize cardiac conduction prolongation, especially in the elderly. The overdose potential of TCAs is greater than with other hypnotic agents, and daytime sedation can be significant.

Trazodone

Trazodone is a potent sedating antidepressant. Trazodone improves sleep continuity and is an attractive option in persons prone to substance abuse, as addiction or tolerance is not a problem.[\[57\]](#) Trazodone is also used in conjunction with stimulating antidepressants such as some SSRIs and bupropion in depressed patients with insomnia. Adrenergic blockade can result in oversedation and orthostatic hypotension, especially in elderly patients. The risk of priapism, a condition of painful, prolonged erection in men, is rare. Other antidepressants used include *Mirtazapine* due to its sedative properties. Evidence for their efficacy when used alone is relatively weak and hence no specific agent within this group is recommended as preferable to the others in this group.[\[58-61\]](#)

Antihistamines

Antihistamines are found in many over-the-counter (OTC) sleep aids. These agents are effective for mild insomnia; however, next-day sedation may be a problem. Antihistamines commonly cause psychomotor impairment and anticholinergic effects. Tolerance may also develop with repeated use and evidence for their efficacy and safety is very limited.[\[62\]](#)

Alternative medications

These are drugs with variable evidence and are useful only in individual cases.

Valerian is a perennial plant that appears to increase GABA concentrations in animal studies, but its exact mechanism is not known. Valerian should not be used for the acute management of insomnia because its hypnotic effect is delayed for 2–4 weeks. Valerian appears to be well tolerated; however, it can cause headache and daytime sedation[63] and is currently still being evaluated.[64]

Other herbs used to promote sleep include skullcap, passion flower, California poppy, and Lemon balm.[65] Melatonin and L-tryptophan are two other molecules undergoing evaluation for the treatment of chronic insomnia.[66] There is currently very little evidence for their use.[67] Indiplon, a novel GABA_A potentiator, till recently being studied,[68] has now been abandoned due to its toxicity.

This week the Food and Drug Administration (FDA) announced that several prescription sleep medications now have to carry a “**black box**” **warning** alerting consumers of the potential for serious or life-threatening side effects. This is the agency's most prominent **warning** for medications. May 2, 2019

<https://www.healthline.com/health-news/why-fda-issued-a-black-box-warning-for-sleep-aids-such-as-ambien>

(7) Describe **the extent to which** evidence supports a finding that the use of cannabis alleviates symptoms caused by the medical condition or its treatment. For best results, please cite research, published evidence, or scientific findings AND attach a PDF copy to your submittal. Indicate specific lines, page, section. Please use standard AMA format as outlined in the instructions.

1. <http://doi.org/10.1002/cbdv.200790150>

Sativex patients and their caregivers have remarked to their physicians how the medicine had transformed their lives through its ability to allow them more restful sleep, increase their daytime level of function, and markedly improve their quality of life. Its addition to the pharmacopoeia may be welcomed by patients, families, and physicians.

2. <https://harmreductionjournal.biomedcentral.com/articles/10.1186/1477-7517-2-18>

Approximately three quarters of participants (71%) claimed to have experienced a return of their symptoms or condition on stopping cannabis, especially: pain (53% of those who claimed a return of symptoms), depression or anxiety (30%), insomnia (11%), spasm (10%) and nausea/vomiting or lack of appetite (9%).

Positive ratings were ("great" or "good" relief) were also typical for its ability to relieve specific symptoms (Table 3). In addition, several other symptoms were noted, primarily insomnia (13% used for insomnia; of these 82% derived "great" relief).

3. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3998228/>

Ninety-seven per cent of respondents used cannabis primarily for chronic pain. Average pain improvement on a 0–10 pain scale was 5.0 (from 7.8 to 2.8), which translates to a 64% relative decrease in average pain. Half of all respondents also noted relief from stress/anxiety, and nearly half (45%) reported relief from insomnia. Most patients (71%) reported no adverse effects, while 6% reported a cough or throat irritation and 5% feared arrest even though medical cannabis is legal in Hawai'i. No serious adverse effects were reported.

These results suggest that Cannabis is an extremely safe and effective medication for many chronic pain patients. Cannabis appears to alleviate pain, insomnia, and may be helpful in relieving anxiety. Cannabis has shown extreme promise in the treatment of numerous medical problems and deserves to be released from the current Schedule I federal prohibition against research and prescription.

4. <http://doi.org/10.1016/j.smr.2007.12.004>

Several studies have shown that acute administration of THC decreases sleep latency,³⁸ and is associated with reports of greater ease in getting to sleep

5. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3929256/>

In addition, sleep improvement appears to be a primary motivator for coping-oriented use. Additional research is needed to examine the health consequences of this pattern of cannabis use and whether alternative sleep promoting interventions (e.g. CBT-I) could reduce the reliance on cannabis for adequate sleep among those with PTSD.

6. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3673028/>

Mental health disorders were the next largest group of diagnoses made (22.9%), followed closely by sleep disorders (21.3%).

Non-prescription therapies tried by applicants seeking medicinal marijuana allowances included physical therapy (48.6%), chiropractic services (37.2%), surgery (21.9%), psychological counseling (20.7%), and acupuncture (19.6%). Thus, these data do not suggest that applicants immediately seek marijuana recommendations as the first strategy to deal with their symptoms. In many cases, these individuals tried more traditional forms of medicine.

7. <https://www.ncbi.nlm.nih.gov/pubmed/26195653>

While further research into cannabinoid treatment effects on PTSD symptoms is required, the evaluated evidence indicates that substantial numbers of military veterans with PTSD use cannabis or derivative products to control PTSD symptoms, with some patients reporting benefits in terms of reduced anxiety and insomnia and improved coping ability.

8. [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(00\)30567-0/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(00)30567-0/fulltext)

I prescribed the cannabis simply with a view to utilizing a well-known remedy for insomnia, but it did much more than procure sleep.

9. <https://www.ncbi.nlm.nih.gov/pubmed/12185373>

In a survey of 15 chronic pain patients who admitted to using cannabis medicinally pain, sleep and mood were most frequently improved, while doses used were modest.

Small doses of smoked cannabis may improve pain, mood and sleep in some patients with chronic pain.

10. <http://doi.org/10.1213/ANE.0b013e3181c76f70>

Thirty-one subjects were enrolled and 29 completed the trial (26 women, mean age 49.5 yr). Although sleep was improved by both amitriptyline and nabilone, nabilone was superior to amitriptyline (Insomnia Severity Index difference = 3.2; 95% confidence interval = 1.2-5.3). Nabilone is effective in improving sleep in patients with FM and is well tolerated. Low-dose nabilone given once daily at bedtime may be considered as an alternative to amitriptyline.

11. <http://www.health.state.mn.us/topics/cannabis/about/firstyearreport.html>

At this point, the safety profile of the medical cannabis products available through the Minnesota program seems quite favorable. Approximately 20-25% of enrolled patients report negative physical or mental side effects of some kind, with the majority – around 60% - reporting only one and 90% reporting three or fewer. The vast majority of adverse side effects, around 90%, are mild to moderate in severity. An assessment of the 30 patients reporting severe side effects, meaning “interrupts usual daily activities,” found no apparent pattern of patient age, medical condition, or type of medical cannabis used. The most common adverse side effects are dry mouth, drowsiness, and fatigue. Fortunately, up to the present no serious adverse events (life threatening or requiring hospitalization) have been reported.

12. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4845302/>

Studies examining the effect of cannabis on objective sleep measurements obtained either by an experienced observer rating sleep by polysomnography (PSG) largely confirm the subjective reports. For instance, an observer-rated study showed that administration of 10, 20, or 30 mg of THC decreased total time to fall asleep, and a PSG study showed both shorter sleep latency (SL), and decreased time awake after sleep onset (WASO).

13. <https://www.ncbi.nlm.nih.gov/pubmed/28749704>

At Time 1, 25% of students reported using at least one substance (alcohol, marijuana, or over-the-counter medications) for sleep aid in the past two weeks.

14. <https://www.ncbi.nlm.nih.gov/pubmed/4337346/>

Although subjective effects of oral THC are reported to appear within 30 to 60 minutes, the increment in Stage 4 sleep suggests that the onset of drug action occurred about 3 hours after ingestion. These observations indicate the insensitivity of the latency to sleep onset measure to any initial hypnotic properties of THC, since subjects were asleep well before the drug could have taken effect. The decrease in time spent awake after sleep onset and the increase in Stage 4 sleep, however, could be interpreted as indicating, respectively, less disturbed and "deeper" sleep, thereby empirically supporting the attribution of sedative properties to THC.

15. <http://doi.org/10.1016/j.neuropharm.2011.08.013>

Patients with post-traumatic stress disorder (PTSD) frequently complain of having sleep disturbances, such as insomnia and rapid eye movement (REM) sleep abnormality. Cannabidiol (CBD), a psycho-inactive constituent of marijuana, reduces physiological non-REM (NREM) sleep and REM sleep in normal rats, in addition to generating its anxiolytic effect.

16. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5101100/>

Cannabidiol oil, an increasingly popular treatment of anxiety and sleep issues, has been documented as being an effective alternative to pharmaceutical medications. This case study provides clinical data that support the use of cannabidiol oil as a safe treatment for reducing anxiety and improving sleep in a young girl with posttraumatic stress disorder.

17. <https://www.ncbi.nlm.nih.gov/pubmed/24095000>

Patients reported using cannabis to treat multiple symptoms, with sleep, pain, and anxiety being the most common. Cannabis was perceived to provide effective symptoms relief across medical conditions. Patterns of use were also consistent across medical conditions. Notable differences were observed with regard to modes of access.

18. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4758425/>

Marijuana was customarily used to treat insomnia and as an antiemetic before the onset of specific therapies in the 1930s.

19. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1654142/>

Cannabis, in herbal form, is widely used as self-medication by patients with diseases such as HIV/AIDS and multiple sclerosis suffering from symptoms including pain, muscle spasticity, stress and insomnia.

21. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3068013/>

Even less attention has focused on inhaled "street" cannabis. Data show that 36%–43% of patients with MS have at some time smoked cannabis. The figure for current use, 14%–18%, is more modest, but indicates that a substantial minority of patients with MS find cannabis helpful for relief from pain, spasticity, insomnia, bladder problems, tremors, and emotional distress.

22. <https://www.ncbi.nlm.nih.gov/pubmed/15184623/>

The symptoms reported by medical cannabis users to be most effectively relieved were stress, sleep, mood, stiffness/spasm, and pain.

23. <http://doi.org/10.1016/j.jns.2008.06.037>

The VAS evaluation of self-reported clinical modifications after cannabis medicinal use showed a wide range of improvement that was mainly perceived in sleep disturbances, pain, tremor, and muscle spasms

24. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4578915/>

Many people suffering from PTSD often have interrupted sleep, with many seeking medical marijuana as a means of helping them treat their sleep issues

25. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4157067/>

Our survey reports that cannabidiol-enriched cannabis is behaviorally well tolerated and may have beneficial effects on cognition and mood. Many parents reported that their children experienced better sleep, increased alertness, and better mood while taking cannabidiol-enriched cannabis. These beneficial side effects are rarely reported with pediatric use of other AEDs (anti epileptic drugs).

26. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5312634/>

Finally, preliminary clinical trials suggest that high-dose oral CBD (150–600 mg per day) may exert a therapeutic effect for epilepsy, insomnia, and social anxiety disorder. Nonetheless, such doses of CBD have also been shown to cause sedation.

27. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5165161/>

In addition, we have assessed the role of the cannabinoid system and marijuana constituents in neuroprotection as well as considered other beneficial effects of marijuana. Marijuana has been shown to improve nonmotor symptoms of PD such as depression, pain, sleep, and anxiety. Moreover, components of cannabis have been demonstrated to have neuroprotective effect due to their anti-inflammatory, antioxidative, and antiexcitotoxic properties.

Effect of Cannabinoids on Sleep Disorders

Sleep disorders are common in PD patients and negatively affect the quality of life. The reported prevalence ranges from 25% to 98% and this wide variation could be due to differences in study design and diagnostic tools used [297]. The causes of the sleep disturbances in PD are multifactorial and include neurodegeneration and the medications used to treat motor symptoms of PD [298]. Various sleep disorders including rapid eye movement sleep behavior disorder, insomnia, sleep fragmentation, excessive daytime sleepiness, restless legs syndrome, and obstructive sleep apnea have been described in PD patients [2 99 , 300].

Cannabidiol, the major nonpsychotic component of marijuana, has been reported to improve rapid eye movement sleep behavior disorder in PD patients [68 , 6 9]. Marijuana has also been shown to improve nonmotor symptoms of PD including sleep [65]. In clinical trials involving 2000 patients with various pain conditions, nabiximols has been demonstrated to improve subjective sleep parameters [3 01]. Thus, marijuana could be used to enhance the quality of life of PD patients by alleviating sleep disorders and pain.

28. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4604191/>

The 1854, the US Dispensary listed cannabis to treat neuralgia, depression, pain, muscle spasms, insomnia, tetanus, chorea, insanity, and other disorders.

29. <https://www.ncbi.nlm.nih.gov/pubmed/26317379>

367 medical marijuana patients in Arizona were surveyed.

145 patients reported using medical marijuana for treatment of Insomnia.

31 patients reported using medical marijuana for treatment of Sleep Apnea.

General relief from Insomnia symptoms was 82.7% and 58.1% for Sleep Apnea

Relief by medical marijuana compared to other medications was 77.4% for Insomnia and 85% for Sleep Apnea.

Less frequent use of other medications was 81.9% for Insomnia and 66.6% for Sleep Apnea.

30. <https://www.ncbi.nlm.nih.gov/pubmed/28189912>

In regards to conditions, pain-related conditions were the most common, reported by 53% of participants (n = 144; chronic pain 36%; (n = 98), arthritis 12% (n = 32), headache 5% (n = 14)). The second most prominent class was mental health (eating disorder, PTSD & psychiatric disorder), reported by 15% (n = 41). Other prominent conditions included gastrointestinal disorders (11%, n = 29), insomnia (7%, n = 18) and multiple sclerosis (4%, n = 11).

In regards to symptoms; the most highly endorsed were chronic pain (73%, n = 197), stress (60%, n = 162), insomnia (57%, n = 155), depression (46%, n = 126) and headache (32%, n = 87). Gastrointestinal (GI) issues also featured prominently, with 29% (n = 79) citing appetite loss and another 29% (n = 79) nausea. Cannabis was perceived to be very effective at symptom relief, with 95% (n = 257) reporting that it “often” or “always” helped alleviate their symptoms.

31. <http://doi.org/10.1111/j.1742-1241.2004.00271.x>

Over the period 1998–2002, 3663 questionnaires were distributed, and 2969 were returned (81% response rate).

14 patients reported using medical marijuana to treat Insomnia for (1–8) years.

Overall Effectiveness. Of 948 reported users, 648 (68%) reported that cannabis made their symptoms overall much better, 256 (27%) said a little better, 36 (4%) said no difference and eight subjects said a little worse (four subjects) or much worse (four subjects).

Effectiveness Compared to Other Medications. When asked how cannabis compared to other medications overall, 412 of 916 subjects (45%) said it worked much better than prescribed medications, 261 (28%) said it was somewhat better and 45 (5%) said it was about the same; only 27 subjects said that prescription medicines worked better than cannabis (18 somewhat better and nine much better). One hundred and seventy-one (19%) subjects said it was impossible to tell.

Side Effects Compared to other Medications. When asked to compare the undesirable effects of cannabis to those of prescribed medicines, 872 subjects responded, of whom six found that cannabis produced much worse side effects, 23 found somewhat worse side effects and 54 said the side effects were about the same. Two hundred and sixty-four (30%) subjects stated that side effects of prescribed medicines were somewhat worse and 294 (34%) said they were much worse. Two hundred and thirty-one (26%) stated that it was impossible to tell.

Effects on Other Medication Use. Of the 909 subjects responding to this question, 374 stated that their use of cannabis had changed their use of other medications, while 521 said it had not. Fourteen were not coded.

Return of Symptoms on Stopping. Of the 876 subjects responding, 673 said their symptoms returned or got worse when they stopped using cannabis, and 203 denied any worsening on stopping cannabis.

32. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4277530/>

Most of the respondents (from the clinic and online groups) reported that cannabis improved their mood, pain, muscle spasms, and sleep .

33. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2683812/>

Sleep problems

Nine teens in our sample described using marijuana to help them sleep. The "trouble" they had with sleeping was a constant problem that many had experienced for years. One 16-year old, who also experienced mild depression, indicated that she "stopped sleeping for two years." Not only did the problem affect their school performance, but it was deeply disturbing to them.

As another female described,

"I have a really hard time sleeping. I can lay there for about four to five hours, just laying there. And I just finally had it, and I just feel like screaming I don't want to wake anyone up. So I go downstairs and ask my gran or my brother [for some marijuana] or I have a roach or two sitting around." [16 years, non-daily use]

Although one teen indicated that she had spoken to her mother about her problems sleeping, others indicated that the adults in their lives did not offer any support.

"I have trouble going to sleep and waking up... My mum wanted to get the doctor to put me on sleeping pills but he said at such a young age it would cause like an addiction to them. ..I've had these problems since elementary school...I just, I can't go to sleep at night and then I like to sleep during the day." [Female, 14 years, non-daily use]

Many teens turned to pot and found almost immediate benefits in helping them sleep. Likened to a "magic sleeping pill" by one young male, the teens found it calmed their "busy minds," helped them relax and fall asleep quickly.

34. <https://www.ncbi.nlm.nih.gov/pubmed/11210205>

This article reports on an exploratory study of medical cannabis users. Interviews were completed with 50 self-identified medical cannabis users recruited through notices in newspapers and on bulletin boards. They reported using cannabis for a variety of conditions including HIV-AIDS-related problems, chronic pain, depression, anxiety, menstrual cramps, migraine, narcotic addiction as well as everyday aches, pains, stresses and sleeping difficulties .

35. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3480566/>

There are no studies on marijuana for treating RLS, but there is considerable anecdotal evidence from patients as to its effectiveness. Typically, only 1 or 2 puffs of a marijuana cigarette or vaporizer is sufficient to relieve RLS symptoms. It is not clear how long the relief lasts, as most patients use this at bedtime, but they do report the very rapid disappearance of their symptoms, which then helps them fall asleep.

36. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4537525/>

These findings suggest that tolerance to the somnolent effects of THC may have occurred, but results should be considered preliminary due to design limitations.

37. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5053383/>

A 57-year-old, married male patient reporting fibromyalgia for 5 years, and osteoarthritis, torn shoulder tendon, and spinal stenosis for over 20 years was referred to our clinic. His initial in-clinic recorded pain score was 8/10 on a numerical rating scale. The patient also had a history of severe obesity, sleep apnea, restless legs syndrome, and anxiety. Signs of neuropathic pain included widespread allodynia and positive DN4 score. At the time of meeting, the patient was taking several prescribed pain medications, including Percocet 5/325 mg as needed and Oxyneo 40 mg daily. Physiotherapy, corticosteroid injections, codeine, and a number of anti-inflammatory medications were unsuccessful at achieving adequate analgesia. The patient was inexperienced with cannabis, except for intermittent use on weekends.

The patient was prescribed 1.5 g per day of a strain of cannabis containing 5% THC and 8% CBD to be administered by a vaporizer. After 2 weeks of trial, the patient reported a lack of success, and a strain of 12% THC was added to the other strain, with instructions to mix the strains in equal parts. At 60 days of follow-up, the patient's pain was lowered to a weekly average of 3/10 on a numerical rating scale, and he lowered his use of Percocet from four pills per day to three pills per week, on average.

38. <https://www.ncbi.nlm.nih.gov/pubmed/15118485>

It would appear that the cannabinoids, THC and CBD, when given in the doses and in the combinations used in the present study, are unlikely to have adverse clinical effects on sleep. THC would appear to be a sedative compound, whereas CBD would appear to have some alerting properties. The distinct activity of these compounds suggests that they could be complementary in clinical practice. The alerting activity of CBD may be particularly useful in the concomitant administration of THC and CBD when the therapeutic activity of both compounds is sought.

99. <https://www.nap.edu/catalog/6376/marijuana-and-medicine-assessing-the-science-base>

Victims of spinal cord injury reporting at IOM workshops noted that smoking marijuana reduces their muscle spasms, their nausea, and the frequency of their sleepless nights.

40. <https://www.nap.edu/catalog/24625/the-health-effects-of-cannabis-and-cannabinoids-the-current-state>

There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols) (4-19)

(8) Provide any information, studies, or research reports regarding any beneficial or adverse effects from the use of cannabis in patients with the medical condition. For best results, please cite research, published evidence, or scientific findings AND attach a PDF copy to your submittal. Indicate specific lines, page, section. Please use standard AMA format as outlined in the instructions.

Minnesota has undertaken the most comprehensive research on the medical cannabis patients in its medical cannabis program. Including surveys by both the patients and their physicians. Tracking which medical cannabis products they purchase, use and

continue using to treat each qualifying condition.

The Minnesota Department of Health publishes reports of the medical cannabis patients and how medical marijuana helps them with insomnia and sleep problems. In its first year of reports, the Minnesota DOH published patient comments about the beneficial effects of the medical marijuana.

<https://www.health.state.mn.us/people/cannabis/about/firstyearreport.html>

(REF #94) <https://www.health.state.mn.us/people/cannabis/docs/about/appendixa.pdf>

☞**My insomnia is so much better**,my muscle spasms have calmed down some,I have an appetite now,my muscle pain has lowered quite a bit to the point I can get some things down around the house,I was walking with a cane but I am no longer at this point...I believe my balance over all is better at this moment in time.

☞With my cancer diagnoses and treatment, I've found relief while taking the cannabis!!! **I get relief from pain, relief from nausea, relief from insomnia.**

Further reports in the following years also track which patients under each condition report benefits of medical marijuana on insomnia and sleep problems.

<https://www.health.state.mn.us/people/cannabis/about/omcreport.html>

<https://www.health.state.mn.us/people/cannabis/about/cohort.html>

(REF #93) https://www.health.state.mn.us/people/cannabis/docs/about/cohort/2015_2016_benefitspse.pdf

The patient self-evaluation is required for patients to complete prior to each medical cannabis purchase. It includes questions to assess symptom severity, some of which are administered to all patients (standard set of 8 symptom measures) and some of which are tailored to symptoms for a given condition (condition-specific symptom measures). Since symptom data is collected prior to each patient's first medical cannabis purchase, symptom changes can be assessed over time and compared to baseline (baseline = patient responses to symptom questions just prior to their first medical cannabis purchase)

These reports are useful to show that medical marijuana patients find a greater than 30% reduction in depression symptoms, and a large percentage of patients continue to maintain that reduction of depression for 4 months.

Of patients included on the standard 8 symptom analysis (n = 1512), more than half experienced moderate to severe symptoms at baseline on all measures except for vomiting(32%).Of patients experiencing moderate to severe symptoms at baseline, anywhere between 36% and 60% achieved at least a 30% reduction in symptom severity (symptom improvement) within 4 months of their first medical cannabis purchase. The lowest proportion of patients reporting symptom improvements in the initial 4-month period were for pain (36%) and fatigue (40%) symptoms, while the greatest proportion of patients reporting symptom improvements were for vomiting (60%), depression (57%), and nausea (56%) symptoms.

(REF #92) https://www.health.state.mn.us/people/cannabis/docs/about/cohort/2016_2017_benefitspse.pdf

(REF #91) https://www.health.state.mn.us/people/cannabis/docs/about/cohort/c2015_2017_benefitspse.pdf

MDOH publishes Adverse Side Effects reports. I urge you to read them all as it shows how small the number of adverse side effects reports are.

<https://www.health.state.mn.us/people/cannabis/about/cohort.html>

(REF #90)

https://www.health.state.mn.us/people/cannabis/docs/about/cohort/appendix_c_2015_2016_patientreportednegativeeffects.pdf

(9) Attach letters of support from physicians or other licensed health care professionals knowledgeable about the medical condition.

See attached

Marghee's Mobile Medical

Margaret Maupin, APRN, FNP

4015 Waha Road, Kalaheo, HI 96741

Phone: (808)635-2082 Website: www.marghee.com

May 26, 2020

Aloha,

My name is Marghee Maupin and I am a board certified family Nurse Practitioner in Hawaii with over 30 years of experience. In the course of my practice, I have treated patients who utilize medical cannabis as an alternative treatment option for multiple health conditions. I have observed, (per patient report), that medical cannabis reduces the symptoms and severity of anxiety, insomnia and depression.

These three diagnosis present commonly as the top conditions that my patient's report medical cannabis has helped them with.

I have discussed, observed and documented the side effects of medical cannabis with my patient's and I have compared the side effects with traditional pharmaceuticals. Generally, I have found medical cannabis to have fewer and more manageable side effects than pharmaceutical formulations.

I am writing this letter as a letter of support to add Anxiety, Insomnia and Depression into the Hawaii Medical Cannabis program.

Please contact me at my office if you require any information.

Sincerely,

A handwritten signature in black ink that reads "M Maupin NP". The signature is fluid and cursive, with the initials "NP" written in a slightly larger, more distinct font at the end.

Margaret Maupin, APRN

Dr. Saqib Nakadar D.O.

37300 Dequindre Rd Ste 110

Phone: 586-983-4200

Internal Medicine

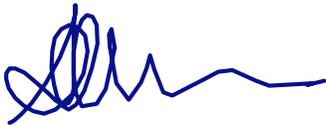
Sterling Heights, MI 48310

Fax: 586-983-4226

May 26, 2020

Dear Review Board,

My name is Dr. Saqib Nakadar, and I am a licensed physician practicing internal medicine. I am writing this letter in support of adding Insomnia to the medical cannabis program. Based on my 10 years of experience treating patients who have chosen to try medical cannabis after trying and failing with traditional prescription and therapy treatments, my patients have reported great success in reducing the severity of Insomnia using medical cannabis.



Dr. Saqib Nakadar D.O.



ASSOCIATION OF CANNABIS SPECIALISTS
SCIENCE. EDUCATION. REGULATION. COMPASSION.

May 27, 2020

Dear Madam/Sir:

I write to you to support the petitions before you to include anxiety, depression, and insomnia as qualifying conditions for medical cannabis treatment in Hawai'i.

I am a cannabis medicine specialist. I went to Harvard Medical School and trained in Internal Medicine at the Brigham & Women's Hospital in Boston. I have been in practice for over 25 years, the last nearly decade exclusively focused on cannabis medicine. I am president of the Association of Cannabis Specialists – an international professional organization, and I am an Instructor of Medicine at Harvard Medical School.

In Massachusetts, where I live and practice, we do not have qualifying conditions per se. We are afforded the freedom to treat patients who have any condition that is medically appropriate to treat with cannabis. I think this is an ideal approach that returns the ability and responsibility to follow the science and medical best practices to the physicians who are best able to judge that medical necessity.

The literature on medical cannabis specifically for the indications of anxiety, depression, and insomnia is clear. These studies have been presented by the petitioner and I would be happy to address any questions about these that you may have. Cannabis can be very effectively used to treat all three of these problems.

Dosing is the critical element dividing success or failure, particularly for these specific conditions. As with any medication, cannabis can be used successfully or it can be misused. Cannabis can be used in conjunction with many conventional medications to achieve better benefit than with either alone. I have personally treated thousands of patients with these specific illnesses, and the results are impressive.

As a practical matter, to improve the outcomes for patients in HI, I would suggest greater requirement of clinicians to be specific about dosing and delivery methods, and absolute adherence by the dispensary agents to a clinician's treatment plan.

777 Concord Ave. Ste 104
Cambridge, MA 02138

800-645-0807
www.cannabis-specialists.org

Please refer to the Association of Cannabis Specialists' website and the document entitled [A Federal Framework of Regulation for Medical Cannabis Use](#) which can equally well be applied to states' programs.

I, and the medical literature, strongly support the addition of anxiety, depression, and insomnia to the list of conditions clinicians are able to treat with medical cannabis in HI. I urge you to add these conditions to the approved list.

Sincerely,



Jordan Tishler MD
President, CMO inhaleMD
President, Association of Cannabis Specialists
Instructor of Medicine, Harvard Medical School

James Berg, MD
PO Box 371
Hawi, HI 96719
808-889-1822
Barefootmd@gmail.com

Aloha,

I am licensed medical doctor from the Big Island of Hawaii, board certified in both Family Medicine and Integrative Medicine. I have been in practice for over thirty years treating my clients with a reasonable balance between medical and natural approaches to healing. I co-direct a school of natural medicine called the *Barefoot Doctors' Academy*, a nonprofit organization operating continuously since 1983, devoted to natural approaches to community medicine. In my career, I have been on the clinical teaching faculty of two medical schools, three traditional oriental medical colleges, two massage schools, and lecturer on scientifically oriented natural medicine. I am writing this letter of support to [REDACTED] three petitions submitted to the Hawaii Department of Health which adds depression, anxiety and insomnia to the medical qualification permitted for medical cannabis certification.

According to my records, I have taken care of over 6,000 patients in Hawaii who have used cannabis legally. I have taken their testimony, examined them, and followed up with many of them at least annually for the past 15 years. I have seen the medical cannabis program go through many changes, and would especially like to thank the Department of Health for their kind and skillful transformation of the Medical Cannabis Program since they took the helm from the Narcotics Enforcement Division. They have worked out many of the administrative kinks and have sincerely honored the clinical necessity of cannabis. A few years ago, they expanded the list of medical qualifications, and recognized Post Traumatic Stress Disorder as a qualification. That was the first psychological condition allowed to that date.

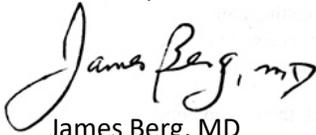
There are many conditions that cannabis is helpful for, but there are three conditions that cannabis is especially helpful for, yet even after twenty years of the program, depression, anxiety and insomnia remain off the qualification list. Cannabis has been labeled in the past as an "euphoric agent" because it relaxes people and helps them feel good. These days we call these kinds of medicines, "antidepressants" and "anti-anxiety medicines". Let me say emphatically, that I recognize that cannabis can cause the very same negative effects in some people. In my experience, at least 90% of my clients already know how cannabis helps their condition. They come and explain to me, their doctor, how it has helped them, and they seek certification so they can use this medicine legally. I want to testify that of all the conditions I have heard the greatest praise for the benefits of cannabis from my clients over the past fifteen years, it has been for this medicine's help with sleep, anxiety and depression. Keeping them off the list seems medically ethical at this point.

[REDACTED] has laid out in detail, various scientific studies giving evidence beyond my anecdotal testimony for these three ailments. I want to support his petition. As a Medical Cannabis Specialist, I witness the answers to these studies every day in my practice. I believe that depression, anxiety and insomnia are the conditions *most helped* by cannabis. I hear, patient after patient, testifying to me how they can finally sleep the night through simply by sucking on a medicated lozenge; How one puff can avert a panic attack; How they finally feel bright spirited and motivated. Cannabis has been a true blessing for many of my patients with insomnia, anxiety or depression, who have been qualified by another condition that the state recognizes. Unfortunately, that list excludes those without severe pain, nausea, muscle spasms, etc.

Yet they still have a severe problem that they know is helped by cannabis. That is self-evident in their experience. We do not need more studies to prove to them that they slept the night through, or didn't escalate into a panic attack, or that they actually feel happy for the first time in a long time. They know it helps with minimal side effects and that is proof enough to them.

In this case, science and politics needs to catch up with the clinical experience. As a practicing physician, I have seen medical cannabis be used far more safely than any pharmaceutical anti-depressant, anti-anxiety med, or sleeping pill commonly prescribed for insomnia, depression and anxiety. One day, I predict that cannabis, or an analogue, will be the medical standard for the first line of attack for mild to moderate depression, anxiety and insomnia. I speak for these sincere patients who already know that cannabis helps them. Please recognize these patient's needs and add depression, anxiety and insomnia onto the list of recognized qualifications for medical cannabis certification.

Sincerely,

A handwritten signature in black ink that reads "James Berg, MD". The signature is written in a cursive, flowing style.

James Berg, MD

HI medical license # 11755

HAWAII ENDOCRINE ASSOCIATES, LLC

TILL HANSEN, M.D.

24 N. Church Street, Suite 403, Wailuku, HI 96793

Telephone: (808) 242-5856 • Fax (808) 242-5949

Email: hawaiiendoc@yahoo.com

Aloha,

I am licensed medical doctor on Maui, board certified in both Internal Medicine and Endocrinology. I have been in practice for over thirty years, 25 in Hawaii. I am writing this letter of support of three petitions submitted to the Hawaii Department of Health which adds depression, anxiety and insomnia to the medical qualification permitted for medical cannabis certification.

A few years ago, the list of medical qualifications was expanded to recognized Post Traumatic Stress Disorder (PTSD). Note that PTSD is a disorder that can manifest with anxiety, depression and sleeplessness. There are many conditions that cannabis is helpful for, but there are three conditions that cannabis is especially helpful for, yet even after twenty years of the program, depression, anxiety and insomnia remain off the list of qualifying conditions.

██████████ has laid out in detail, from various evidence-based scientific sources and studies giving evidence that cannabis is helpful for these three ailments. I want to support his petition. I have been evaluating patients for their 329 cards for over 3 years and have done hundreds of renewals. Virtually 100% of patients have been helped. All use cannabis for the indications they listed but have also found that coincidentally medical marijuana helps with anxiety, depression and insomnia.

In fact, I believe that because of the better safety profile cannabis should be the first-line drug for these conditions. Most anxiolytics are habit forming. Anti-depressants have a warning: "May Cause Suicide". Hypnotics, like Ambien, are also habit forming and are used in combination with alcohol to simulate Rohypnol ("roofie") by rapists. Using cannabis as a safe first-line option will be a paradigm shift for many health care providers, but the approval of these conditions by the DOH will go a long way to legitimizing this point of view.

So far, in my decades as a physician, I have much more harm done with alcohol, hypnotics, opiates and anti-depressants and anxiolytics than with cannabis. In fact, as an urgent care, ER, hospital and ICU physician (before starting my Endocrine practice), I have never attended a single patient due to cannabis.

Please recognize these patient's needs and add depression, anxiety and insomnia onto the list of recognized qualifications for medical cannabis certification. Please call if you have any questions, 808-242-5856.

Thank you for your kind attention,

Till Hansen, M.D.

Hawaii Endocrine Associates, Inc.



Richard Podolny M.D. LLC
1188 Bishop Street, ST E 3306
Honolulu, Hawaii, 96813
Phone 808 524 0754 Fax 808 545 4268
Email: contact@podolnymd.com

5/25/20

To whom it may concern:

I am writing this letter in support of [REDACTED] three petitions submitted to the Hawaii Department of Health, which adds depression, anxiety, and insomnia to the medical qualifications permitted for medical cannabis certification.

The mind and body are connected. The effects of insomnia, depression, and anxiety upon the physical well-being of an individual are significant and well documented. Current pharmaceutical interventions for these conditions can have severe side effects and risks. There is scientific evidence to support the use of medical cannabis for these disorders—a medicine with far less potential for addiction or abuse.

After witnessing the knee jerk, draconian response to the opioid crisis, I am concerned for that moment in time when someone realizes that a severe hypnotics problem also exists. I need to know that when severe restrictions are placed on hypnotics, my patients will have a safe and legal alternative. Medical cannabis is that alternative.

I have learned that if you close one door for a patient to escape their pain—they will find another. If you close or restrict the pharmaceutical options, they WILL find other ways to relieve their suffering. The inclusion of the three diagnoses recommended by [REDACTED] for the use of medical cannabis will provide a far safer option for these vulnerable patients.


Richard Podolny M.D.

Insomnia: Definition, Prevalence, Etiology, and Consequences

Thomas Roth, PhD

Sleep Disorders and Research Center, Henry Ford Hospital Detroit, MI

DEFINITION OF INSOMNIA

The term insomnia is used in a variety of ways in the medical literature and popular press. Most often, insomnia is defined by the presence of an individual's report of difficulty with sleep. For example, in survey studies, insomnia is defined by a positive response to either question, "Do you experience difficulty sleeping?" or "Do you have difficulty falling or staying asleep?" In the sleep literature, insomnia is sometimes used as a term to describe the presence of polysomnographic evidence of disturbed sleep. Thus, the presence of a long sleep latency, frequent nocturnal awakenings, or prolonged periods of wakefulness during the sleep period or even frequent transient arousals are taken as evidence of insomnia.¹ Thus, insomnia has been thought of both as a symptom and as a sign. However, for the purpose of this paper, the term insomnia will be used as a disorder with the following diagnostic criteria: (1) difficulty falling asleep, staying asleep or nonrestorative sleep; (2) this difficulty is present despite adequate opportunity and circumstance to sleep; (3) this impairment in sleep is associated with daytime impairment or distress; and (4) this sleep difficulty occurs at least 3 times per week and has been a problem for at least 1 month.

What qualifies insomnia to be considered a disorder? A disorder is a condition associated with negative consequences, and importantly, these consequences are not a normal result of the condition but rather the result of some sort of pathological response. In the present discussion, the consequences of insomnia can not merely be the normal consequence of sleep loss.

Disclosure Statement

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Address correspondence to: Thomas Roth, PhD, Director of Research, Sleep Disorders and Research Center at Henry Ford Health System, Henry Ford Hospital Sleep Center, 2799 West Grand Blvd., Detroit, MI 48202; Tel: (313) 876-2233; Fax: (313) 916-5150; E-mail: TRoth1@hfhs.org

PREVALENCE OF INSOMNIA

Estimates of the prevalence of insomnia depend on the criteria used to define insomnia and more importantly the population studied. A general consensus has developed from population-based studies that approximately 30% of a variety of adult samples drawn from different countries report one or more of the symptoms of insomnia: difficulty initiating sleep, difficulty maintaining sleep, waking up too early, and in some cases, non-restorative or poor quality of sleep.² Conclusions from the NIH State-of-the-Science Conference held in June 2005 indicate that the addition of a diagnostic requirement that includes perceived daytime impairment or distress as a function of the insomnia symptoms results in approximately 10% prevalence of insomnia.³ Finally, the application of more stringent diagnostic criteria, such as the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*,⁴ which includes the additional requirements that insomnia symptoms persist for at least 1 month and do not exclusively occur in the presence of another sleep disorder, mental disorder, or the direct physiological effects of a substance or medical condition, yields current prevalence estimates of approximately 6%.⁵

Several well-identified risk factors for insomnia were reported by the State-of-the-Science Conference in June 2005.³ Age and gender are the most clearly identified demographic risk factors, with an increased prevalence in women and older adults. While the cause of this increased risk in the elderly is not well defined, it may be due to the partial decline in functionality of sleep control systems that may contribute to insomnia in this older population. Importantly, the presence of comorbid medical conditions is also a significant contributor to the increased prevalence of insomnia in the elderly. Additionally, in women, insomnia is more prevalent with both the onset of menses and menopause.⁶ Comorbid medical disorders,⁷ psychiatric disorders,⁸ and working night or rotating shifts⁹ all represent significant risks for insomnia. It is important to recognize that these factors do not independently cause insomnia, but rather they are precipitants of insomnia in individuals predisposed to this disorder. In fact, chronic illnesses are a significant risk for insomnia. It is estimated that the majority of people with insomnia (approximately 75%-90%) have an increased risk for comorbid medical disorders,⁷ such as conditions causing hypoxemia and dyspnea, gastroesophageal reflux disease, pain conditions, and neurodegenerative diseases. Importantly, a variety of primary sleep disorders as well as circadian rhythm disorders are frequently comorbid with and often lead to insomnia. Among the primary sleep disorders, restless legs syn-

drome (RLS),¹⁰ periodic limb movement disorders (PLMD), and sleep-related breathing disorders (snoring, dyspnea, sleep apnea) often present with an insomnia symptom.¹¹ This is especially true among the elderly. Among younger individuals, difficulty falling asleep is often associated with a phase delay syndrome. However, in the elderly, phase advance syndrome results in reports of difficulty initiating sleep, maintaining sleep, and experiencing early morning awakenings.¹²⁻¹⁴

The most common comorbidities associated with insomnia are psychiatric disorders. It is estimated that 40% of all insomnia patients have a coexisting psychiatric condition.^{8,15} Among these psychiatric disorders, depression is the most common, and insomnia is a diagnostic symptom for depressive and anxiety disorders.¹¹

CONSEQUENCES OF INSOMNIA

Due to its chronicity, insomnia is associated with substantial impairments in an individual's quality of life. In several studies, insomniacs reported decreased quality of life on virtually all dimensions of the 36-item Short Form Health Survey of the Medical Outcomes Study (SF-36), which assesses 8 domains: (1) physical functioning; (2) role limitation due to physical health problems (role physical); (3) bodily pain; (4) general health perceptions; (5) vitality; (6) social functioning; (7) role limitations due to emotional health problems (role emotional); and (8) mental health.¹⁶⁻¹⁸ One study compared SF-36 results in groups of mild and severe insomnia patients with groups of patients diagnosed with depression or congestive heart failure (CHF).¹⁹ Severe insomnia patients had numerically greater loss of function than patients with CHF in reported pain, emotional effects, and mental health effects. Additionally, insomnia patients also reported more physical problems than patients with depression.¹⁹

Research has shown that among the daytime consequences of insomnia, the increased occurrence of accidents poses the greatest health risk. Insomniacs are 2.5 to 4.5 times more likely than controls to have an accident.^{20,21} In a sample of 8,625 community respondents in France, Léger et al. reported that 8% of insomniacs and 1% of non-insomniacs had an industrial accident in the past 12 months.²² Work productivity is also compromised among insomniacs due to work-related problems (ie, higher rates of absenteeism, decreased concentration, and difficulty performing duties). Kuppermann and colleagues²³ found that individuals reporting a current sleep problem were more likely than good sleepers to have decreased job performance and to have been absent from work in the last month due to health problems. Simon and VonKorff²⁴ evaluated insomnia in a staff-model health maintenance organization population (N=1,962). After adjusting for age, gender, and chronic disease, days of restricted activity due to illness and days spent in bed were about twice as common among insomniacs compared with non-insomniacs. Additionally, mean total health care expenditures were 60% higher in the insomnia group relative to the controls.

Population- and clinic-based studies have demonstrated a high rate of psychiatric comorbidities in patients with chronic insomnia. In fact, insomnia is more frequently associated with psychiatric disorders than any other medical illness.²⁵ For example, in the Epidemiologic Catchment Area study, 40% of insomniacs had a comorbid psychiatric disorder compared with 16.4% of those with no sleep complaints.⁸ Additionally, depression and anxiety are the

most common comorbid psychiatric disorders in insomniacs. It has traditionally been assumed that insomnia is secondary to the psychiatric disorder; however, given the chronicity of insomnia, it is possible that in some, if not most, cases the insomnia precedes the psychiatric disorder. In fact, it is possible that insomnia represents a significant risk for the development of a subsequent psychiatric disorder. In a large-scale European population-based study (N=14,915), it was found that insomnia more often preceded rather than followed incident cases of a mood disorder.²⁶ This effect is even more pronounced for relapses of the mood disorder, where in 56.2% of cases, insomnia symptoms preceded symptoms of a mood disorder relapse. In contrast, in chronic insomnia patients with a comorbid anxiety disorder, the first occurrence of anxiety or a relapse preceded insomnia in most instances.

To further understand the relation of sleep and psychiatric disorders, several longitudinal studies have examined the evolution of psychiatric disorders among insomnia patients. These studies used follow-up periods ranging from 1 to 40 years, with the majority using a 1- to 3-year follow-up period. In all of these studies, insomnia has been found to confer a substantial risk for the development of a depressive disorder.^{27,28} Typically, the relative risk was approximately 5 (range 2-40), and in all cases it was statistically significant. While some studies also reported an increased risk for anxiety or drug abuse, neither of these was consistently found. Finally, longitudinal studies in subjects with affective disorders show that depressed patients who experience improvements in sleep will also experience a more rapid antidepressant response; while those patients whose insomnia persists will have a short time to relapse.^{29,30} What is clearly needed are clinical trials to assess the impact of insomnia therapy on incidence of depression as well as the time to relapse in depressed patients who are in remission.

The question then arises as to whether insomnia causes depression, vice versa, or both. The close association of insomnia with depression is likely related to common underlying pathophysiological mechanisms for sleep and mood regulation that make the individual vulnerable to both conditions. Data have shown that both the diagnosis of insomnia and the severity of the sleep disturbance are related to overactivation of the hypothalamic-pituitary-adrenal (HPA) axis and the hypersecretion of cortisol.³¹ Recent evidence suggests that there may be some neuroendocrine and clinical similarities between insomnia and depression. Corticotropin-releasing factor (CRF) dysregulation has been implicated in the pathogenesis of psychiatric disorders such as depression³² as well as in the mediation of hyperarousal seen in primary insomnia.³³ This abnormality might represent the common risk factor, and therefore, it is quite possible that both disorders would respond to the same therapeutic intervention (eg, corticotropin-releasing hormone antagonists).

PATHOPHYSIOLOGY OF INSOMNIA

Insomnia is thought to be a disorder of hyperarousal experienced throughout the entire day. This hyperarousal may exhibit itself as a state of hypervigilance during the day and difficulty initiating and maintaining sleep at night.^{34,35} This arousal is currently explained by both cognitive and physiological models of insomnia. The cognitive model suggests that worry and rumination about life stresses disrupt sleep, creating acute episodes of insomnia, especially in initiating sleep and returning back to sleep

after an awakening.³⁶ Then, once an individual begins to experience sleep difficulties, worry and rumination shift from life events to worries about sleep itself and about the daytime consequences of not getting enough sleep. This negatively-toned cognitive activity is further fueled if a sleep-related threat is detected or a sleep deficit is perceived.

In parallel with the cognitive models, another model of the evolution of insomnia proposes that hyperarousal is primarily due to physiologic or neurophysiologic factors. Physiological arousal has been evaluated through measurements of the whole body metabolic rate, heart rate variability, neuroendocrine measures, and functional neuroimaging. Whole body metabolic rate may be measured by oxygen consumption (VO₂). Recent studies compared good sleepers with patients diagnosed with insomnia. The insomnia patients exhibited significantly higher metabolic rates (measured at intervals across the 24-hour day) than the healthy controls. Heart rate variability may provide a measure of arousal in that it is regulated by both sympathetic and parasympathetic nervous system activities. A 36-hour study³⁷ found that average heart rates were increased and variability was decreased in all stages of sleep in insomnia patients compared to healthy normal sleepers.

The neuroendocrine system may also provide evidence of arousal as demonstrated by chronic activation of the stress response system. Several studies measuring 24-hour urinary free cortisol excretion have found high levels in poor sleepers.^{38, 39} Urinary free cortisol levels have also been positively correlated with total wake time, and urinary catecholamines have been correlated with stage 1 sleep percentage and wake time after sleep onset.^{38, 40} Plasma measures of cortisol and adrenocorticotropic hormone (ACTH) have been evaluated in insomnia patients and healthy normal sleepers. Although the evidence is somewhat mixed, primary insomniacs appear to have higher levels of these compounds in their plasma, with the most significant differences seen in the evening and the first half of the night.^{38,39,41} Both the urinary and plasma measures of cortisol and ACTH suggest that the HPA axis is associated with the pathology of chronic insomnia.

Finally, positron emission tomography (PET) has been used to assess cerebral glucose metabolism, an indirect measure of whole brain metabolism, in patients with insomnia.⁴² Compared to healthy subjects, patients with insomnia exhibited greater cerebral glucose metabolism during waking and non-rapid eye movement (REM) sleep states. Furthermore, the insomnia patients demonstrated smaller reductions in relative metabolism from waking to non-REM sleep in wake-promoting regions of the brain. These findings suggest interacting neural networks involved in the inability to fall asleep, which include a general arousal system, an emotion-regulating system, and a cognitive system.

CONCLUSION

Chronic insomnia is highly prevalent and affects approximately 30% of the general population. Insomnia impairs cognitive and physical functioning and is associated with a wide range of impaired daytime functions across a number of emotional, social, and physical domains. Compared with good sleepers, people with persistent sleep disturbances are more prone to accidents, have higher rates of work absenteeism, diminished job performance, decreased quality of life, and increased health care utilization. Various risk factors associated with increased prevalence of chronic insomnia include older age, female gender, and comorbid medical and psy-

chiatric conditions. Approximately 40% of adults with insomnia also have a diagnosable psychiatric disorder—most notably depression. A comorbid psychiatric disorder such as depression or anxiety may be a consequence of—as well as a risk factor for—disrupted sleep. Recent research suggests that insomnia and depression share common pathological processes that make individuals vulnerable to both conditions—specifically, abnormal regulation of CRF. CRF regulation has been extensively implicated in the pathogenesis of depression, and hyperactivity of the HPA axis and CRF neurons could account for the hyperarousal and sleep disturbances associated with chronic insomnia. Studies that improve the knowledge of the neurobiological mechanisms controlling regulation of sleep homeostasis, circadian rhythms, physiological hyperarousal, genetics, stress, and cognition are needed to adequately evaluate the causes and mechanisms of insomnia. Effective pharmacologic and behavioral interventions to treat insomnia rely on accurate neurobehavioral and neurobiological information.

REFERENCES

1. Sateia MJ, Doghramji K, Hauri PJ, Morin CM. Evaluation of chronic insomnia. An American Academy of Sleep Medicine review. *Sleep* 2000;23:243-308.
2. Ancoli-Israel S, Roth T. Characteristics of insomnia in the United States: results of the 1991 National Sleep Foundation Survey. I. *Sleep* 1999;22 Suppl 2:S347-53.
3. National Institutes of Health State of the Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults, June 13-15, 2005. *Sleep* 2005;28:1049-57.
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th Ed. Text Revision. DSM-IV-TR. Washington, D.C.: APA, 1994:551-7.
5. Ohayon MM. Prevalence of DSM-IV diagnostic criteria of insomnia: distinguishing insomnia related to mental disorders from sleep disorders. *J Psychiatr Res* 1997;31:333-46.
6. Johnson EO, Roth T, Schultz L, Breslau N. Epidemiology of DSM-IV insomnia in adolescence: lifetime prevalence, chronicity, and an emergent gender difference. *Pediatrics* 2006;117:e247-56.
7. Katz DA, McHorney CA. Clinical correlates of insomnia in patients with chronic illness. *Arch Intern Med* 1998;158:1099-107.
8. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA* 1989;262:1479-84.
9. Roth T, Roehrs T. Insomnia: epidemiology, characteristics, and consequences. *Clin Cornerstone* 2003;5:5-15.
10. Phillips B, Hening W, Britz P, Mannino D. Prevalence and correlates of restless legs syndrome: results from the 2005 National Sleep Foundation Poll. *Chest* 2006;129:76-80.
11. Ancoli-Israel S. The impact and prevalence of chronic insomnia and other sleep disturbances associated with chronic illness. *Am J Managed Care* 2006;12:S221-9.
12. Avidan AY. Sleep changes and disorders in the elderly patient. *Curr Neurol Neurosci Rep* 2002;2:178-85.
13. Avidan AY. Sleep in the geriatric patient population. *Semin Neurol* 2005;25:52-63.
14. Dement W, Richardson G, Prinz P, Carskadon M, Kripke O, Czeisler C. Changes of sleep and wakefulness with age. In: Finch C, Schneider EL, eds. *Handbook of the Biology of Aging*. 2nd ed. New York: Van Nostrand Reinhold, 1996.
15. McCall WV. A psychiatric perspective on insomnia. *J Clin Psychiatry* 2001;62 Suppl 10:27-32.
16. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993;31:247-63.

17. McHorney CA, Ware JE, Jr., Rogers W, Raczek AE, Lu JF. The validity and relative precision of MOS short- and long-form health status scales and Dartmouth COOP charts. Results from the Medical Outcomes Study. *Med Care* 1992;30:MS253-65.
18. McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care* 1994;32:40-66.
19. Katz DA, McHorney CA. The relationship between insomnia and health-related quality of life in patients with chronic illness. *J Fam Pract* 2002;51:229-35.
20. Balter MB, Uhlenhuth EH. New epidemiologic findings about insomnia and its treatment. *J Clin Psychiatry* 1992;53 Suppl:34-9.
21. National Sleep Foundation. Sleep in America: A survey of US adults. A report prepared by the Gallup Organization for the National Sleep Foundation. Los Angeles, CA: National Sleep Foundation; 1991.
22. Leger D, Guilleminault C, Bader G, Levy E, Paillard M. Medical and socio-professional impact of insomnia. *Sleep* 2002;25:625-9.
23. Kuppermann M, Lubeck DP, Mazonson PD, Patrick DL, Stewart AL, Buesching DP, Fifer SK. Sleep problems and their correlates in a working population. *J Gen Intern Med* 1995;10:25-32.
24. Simon GE, VonKorff M. Prevalence, burden, and treatment of insomnia in primary care. *Am J Psychiatry* 1997;154:1417-23.
25. Benca RM. Consequences of insomnia and its therapies. *J Clin Psychiatry* 2001;62 Suppl 10:33-8.
26. Ohayon MM, Roth T. Place of chronic insomnia in the course of depressive and anxiety disorders. *J Psychiatr Res* 2003;37:9-15.
27. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry* 1996;39:411-18.
28. Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ. Insomnia in young men and subsequent depression. The Johns Hopkins Precursors Study. *Am J Epidemiol* 1997;146:105-14.
29. Perlis ML, Giles DE, Buysse DJ, Tu X, Kupfer DJ. Self-reported sleep disturbance as a prodromal symptom in recurrent depression. *J Affect Disord* 1997;42:209-12.
30. Fava GA, Grandi S, Canestrari R, Molnar G. Prodromal symptoms in primary major depressive disorder. *J Affect Disord* 1990;19:149-52.
31. Richardson GS, Roth T. Future directions in the management of insomnia. *J Clin Psychiatry* 2001;62 Suppl 10:39-45.
32. Gold PW, Chrousos GP. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Mol Psychiatry* 2002;7:254-75.
33. Roth T, Roehrs T, Pies R. Insomnia: pathophysiology and implications for treatment. *Sleep Med Rev* 2007;11:71-9.
34. Bonnet MH, Arand DL. 24-Hour metabolic rate in insomniacs and matched normal sleepers. *Sleep* 1995;18:581-8.
35. Stepanski E, Zorick F, Roehrs T, Young D, Roth T. Daytime alertness in patients with chronic insomnia compared with asymptomatic control subjects. *Sleep* 1988;11:54-60.
36. Harvey AG. A cognitive model of insomnia. *Behav Res Ther* 2002;40:869-93.
37. Bonnet MH, Arand DL. Heart rate variability in insomniacs and matched normal sleepers. *Psychosom Med* 1998;60:610-5.
38. Vgontzas AN, Bixler EO, Lin HM, Prolo P, Mastorakos G, Vela-Bueno A, Kales A, Chrousos GP. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. *J Clin Endocrinol Metab* 2001;86:3787-94.
39. Vgontzas AN, Tsigos C, Bixler EO, Stratakis CA, Zachman K, Kales A, Vela-Bueno A, Chrousos GP. Chronic insomnia and activity of the stress system: a preliminary study. *J Psychosom Res* 1998;45:21-31.
40. Vgontzas AN, Bixler EO, Papanicolaou DA, Kales A, Stratakis CA, Vela-Bueno A, Gold PW, Chrousos GP. Rapid eye movement sleep correlates with the overall activities of the hypothalamic-pituitary-adrenal axis and sympathetic system in healthy humans. *J Clin Endocrinol Metab* 1997;82:3278-80.
41. Riemann D, Klein T, Rodenbeck A, Feige B, Horny A, Hummel R, Weske G, Al-Shajlawi A, Voderholzer U. Nocturnal cortisol and melatonin secretion in primary insomnia. *Psychiatry Res* 2002;113:17-27.
42. Nofzinger EA, Buysse DJ, Germain A, Price JC, Miewald JM, Kupfer DJ. Functional neuroimaging evidence for hyperarousal in insomnia. *Am J Psychiatry* 2004;161:2126-8.

CASE REPORT

Zolpidem-Induced Sleepwalking, Sleep Related Eating Disorder, and Sleep-Driving: Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography Analysis, and a Literature Review of Other Unexpected Clinical Effects of Zolpidem

Romy Hoque, M.D.; Andrew L. Chesson, Jr., M.D.

Sleep Disorders Center; Department of Neurology, Louisiana State University School of Medicine, Shreveport, LA

Zolpidem is a hypnotic which acts at the GABA_A receptor and is indicated for short-term insomnia. Sleep related disorders including somnambulism, sleep related eating and sleep-driving have been reported with zolpidem. A 51-year-old insomniac who used zolpidem 10 mg nightly starting at 44 years of age is described. A few weeks after starting zolpidem she began walking, eating, and had one episode of driving while asleep. Episodes of sleep related eating, sleepwalking, and sleeptalking occurred 3 nights per week, 1 to 2 h after sleep onset. After her evaluation, the patient's zolpidem was gradually discontinued, and all sleep related activities immediately ceased. An 18F-FDG-PET was obtained 2 months after discontinuation of zolpidem. The following day, FDG was administered 1 h after oral administration of

10 mg zolpidem, and then a second PET was performed. We report the results and a review of the literature regarding other unintended effects seen with zolpidem use.

Keywords: Zolpidem, fluorine-18-fluorodeoxyglucose positron emission tomography, sleep related eating disorder, sleepwalking, sleep-driving

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Sleepwalking or somnambulism, is a parasomnia consisting of a series of complex behaviors usually initiated during arousals from slow wave sleep and commonly culminate in walking with an altered state of consciousness and impaired judgment.¹ Sleep related eating disorder (SRED) consists of recurrent episodes of involuntary eating during arousals from sleep.¹ Parasomnias such as sleepwalking, SRED, and sleep-driving can coexist and are rare side effects of zolpidem. In a 2005 National Institutes of Health consensus statement for the treatment of chronic insomnia in adults zolpidem was considered a hypnotic with limited risk.² Two post-marketing studies of zolpidem reported sleepwalking incidences of 7 of 1972 patients (0.3%)³ and 1 of 96 patients (1%).⁴ We present a patient with zolpidem-induced sleepwalking, SRED, and sleep-driving. A fluorine-18-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) was obtained one month after discontinuation of zolpidem. A second 18F-FDG-PET was acquired the following day, 1 h after oral administration of zolpidem 10 mg (Figure 1). The cerebral glucose metabolism rates of the 2 studies were then compared, using statistical parametric mapping analysis. We also review the literature regarding unintended effects of zolpidem use.

CASE REPORT

The patient is a 51-year-old African American woman with past medical history of hypertension, mild obstructive sleep apnea, hyperlipidemia, and depression. Previous diagnostic polysomnogram revealed an apnea-hypopnea index of 10 events/h. Medications included paroxetine 20 mg once a day, extended release metoprolol 25 mg twice per day, and simvastatin 40 mg once a day. History for alcohol, tobacco, or illicit drug use was negative. The patient reported no personal or family history of sleepwalking or other parasomnias. The patient did not have a history of daytime eating disorder. At age 44 the patient was started on non-extended release zolpidem 10 mg at bedtime for insomnia. A few weeks after starting zolpidem, she began sleep related walking, eating, and one episode of driving.

Episodes of sleepwalking, SRED, and sleeptalking occurred 3 nights per week, 1-2 h after sleep onset. The patient would speak incoherently using short phrases with her eyes closed and would then open her eyes when questioned by her husband. She would also leave her bedroom to go to her kitchen where she would eat a loaf of bread, cold cereal, or leftover food. The following morning she would have abdominal fullness, find her kitchen messy, and have complete amnesia for the event. The patient would also leave her home and walk on her front porch or on her front lawn. As a preventive measure, she installed nocturnal alarms on her doors to wake her or her family from sleep if she opened one. Other reported events included one occasion of urination in the hallway, and one episode when the patient drove her automobile 10 miles from her home and

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Address correspondence to: Romy Hoque, M.D., Department of Neurology, Louisiana State University School of Medicine, 1501 Kings Highway, Shreveport, LA; Email: romy.hoque@gmail.com

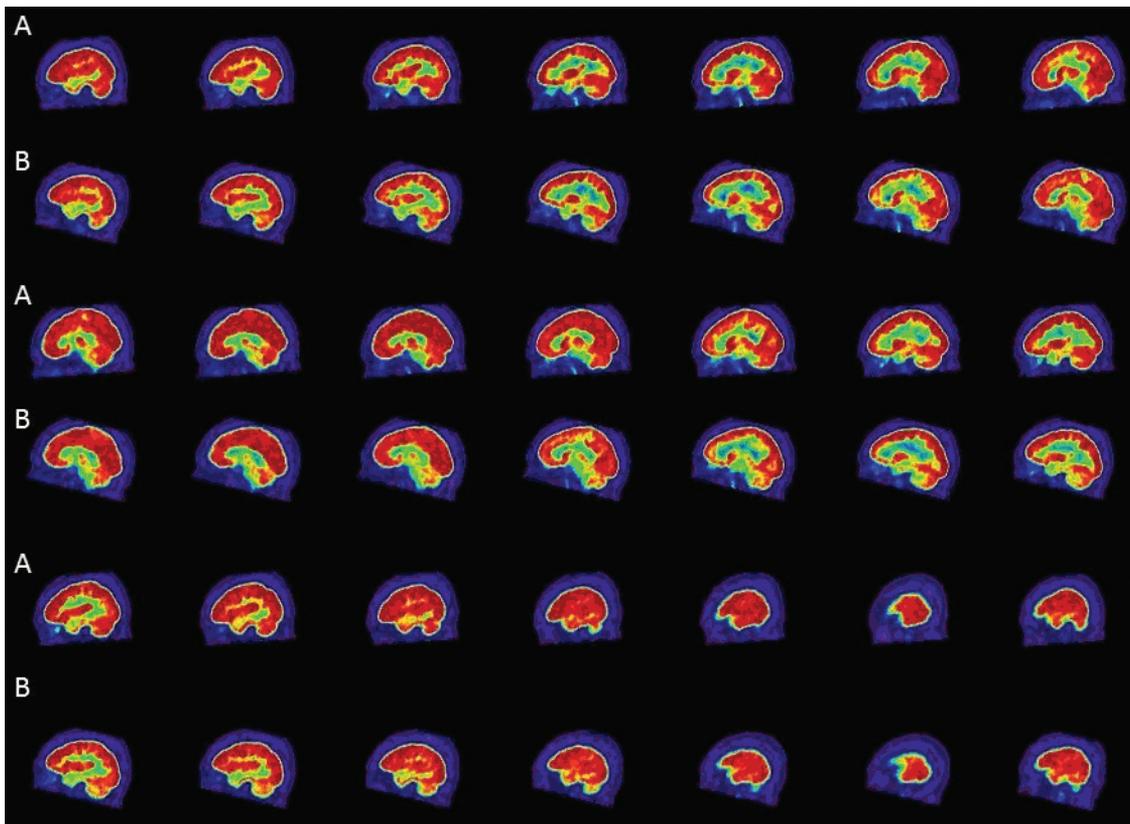


Figure 1—18-fluorine-fluorodeoxyglucose-positron emission tomography (18F-FDG-PET) of a patient with zolpidem induced sleepwalking, sleep related eating disorder, and sleep-driving. A: 18F-FDG-PET off zolpidem. B: 18F-FDG-PET on zolpidem. FDG was administered to patient 1 h after ingestion of 10 mg zolpidem. Statistical parametric mapping comparison of the 2 sequences shows no significant differences.

was found asleep behind the wheel by police. She had a vague recollection of this event, but thought that she was dreaming. After her evaluation, the patient's zolpidem was gradually withdrawn; all sleep related activities immediately ceased and have not recurred during 6 months of follow-up.

18F-FDG-PET Analysis

The first PET study in our patient was performed after discontinuation of zolpidem for 2 months. A second PET study FDG was administered 1 h after the administration of 10 mg zolpidem. The patient was asleep in the scanner during both PET studies. Statistical parametric mapping comparison between our patient's 2 studies demonstrated no significant differences (Figure 1).

DISCUSSION

Zolpidem is an imidazopyridine drug indicated for short-term insomnia at a dosage usually ranging from 5 to 10 mg per day.⁵ Though considered a non-benzodiazepine since its imidazopyridine structure differs from benzodiazepine fusion of benzene and diazepine, zolpidem is a benzodiazepine receptor agonist with high binding affinity for the GABA_A (gamma-amino butyric acid type A) receptor expressing the α_1 subunit. Benzodiazepines and benzodiazepine receptor agonists like zolpidem bind to the GABA_A receptor at sites that are distinct from the GABA binding site, thereby allosterically affecting the activity of the ligand-operated chloride channel.

GABA is the main inhibitory neurotransmitters in the mammalian central nervous system (CNS). GABA_A receptors exist as pentameric protein complexes, assembled from a combination of at least 19 subunits from 7 distinct gene families (α , β , γ , δ , ϵ , θ , and π). Synaptic GABA_A receptors are responsible for modulating benzodiazepine sensitivity and typically contain $\alpha_{1,2,3, \text{ or } 5}$, $\beta_{2 \text{ or } 3}$, and the γ_2 subunits.⁶ GABA_A receptor sensitivity to benzodiazepines is mediated through α subunits. Benzodiazepines bind to synaptic GABA_A receptors containing α_1 , α_2 , α_3 , or α_5 subunits with comparable affinity. The GABA_A receptor expressing the α_1 subunit corresponds to the benzodiazepine ω_1 receptor.⁷ GABA_A receptors containing the α_1 , α_2 , α_3 , or α_5 subunits correspond to ω_2 benzodiazepine receptors. The ω_3 benzodiazepine receptor is not related to the GABA_A receptor. Extrasynaptic GABA_A receptors are primarily composed of $\alpha_{4,6}$ subunits in combination with δ subunits, and are insensitive to benzodiazepines. The current benzodiazepine receptor nomenclature (ω_1 , ω_2 , and ω_3) replaced the previous anatomical localization classification (central benzodiazepine receptor type 1, central BZ-1; central benzodiazepine receptor type 2, central BZ-2; and peripheral benzodiazepine receptor type 3, BZ3) because of the existence of "central" benzodiazepine receptors with peripheral localization, and "peripheral" benzodiazepine receptors with central localization.

Zolpidem was developed as a drug with a structure different from benzodiazepines, allowing affinity for only a given subset of central benzodiazepine receptors resulting in hypnotic properties without additional anticonvulsant and myorelaxant properties of benzodiazepines. In contrast to benzodiazepines

like clonazepam, diazepam and flunitrazepam, which lack selectivity for the ω_1 , ω_2 , or ω_3 benzodiazepine receptor subtypes; zolpidem has a high affinity for ω_1 .⁸

A possible explanation for zolpidem-induced nocturnal events is that after an arousal from sleep into wakefulness, nocturnal activity (i.e., walking, eating, or driving) occurred and was subsequently not recalled after returning to sleep because of the sedation-mediated amnesic properties of zolpidem. Another possibility is that an arousal occurred out of slow wave sleep with the parasomnia occurring in electroencephalographically verifiable sleep. We felt our patient experienced the later, given her incoherent interactions with her husband during her nocturnal events. Patients who do not recall waking events on zolpidem are typically cognitively functional, and retain the ability to speak in coherent short phrases.⁹

Sleepwalking is a relatively common condition affecting 10% of adults.¹ Recently hotels across the United Kingdom reported an increase in the number of hotel guests found to be sleepwalking.¹⁰ Though the incidence of zolpidem induced sleepwalking has been reported to be low, it is possible that many cases of unexplained sleepwalking may be secondary to zolpidem given its widespread use.^{3,4}

Along with sleepwalking, SRED, and sleep-driving parasomnias, zolpidem has been anecdotally reported to produce a range of unexpected beneficial effects. These include improvement in the following conditions: post-stroke Broca's aphasia; blepharospasm; quadriplegia of central pontine myelinolysis; catatonia of schizoaffective disorder; dementia with apraxia; post-anoxic minimally conscious states; bradykinesia, akinesia, and dystonia in Parkinson disease; post-levodopa dyskinesias in Parkinson disease; vertical saccadic eye movements and parkinsonism in progressive supranuclear palsy; restless legs syndrome; post-anoxic spasticity; and spinocerebellar ataxia (Table S1 summarizes the available reports of improvement in varied neurological conditions with zolpidem use). Effects were usually noted within 30 min of ingestion of the non-extended release formulation and lasted for 2 to 4 h, corresponding with a time to peak plasma concentration of approximately 1.2 h and a half-life of approximately 2.5 h.

Zolpidem effects might be mediated through its anti-anxiety effects, its benzodiazepine receptor agonist properties, its GABAergic activity, or some combination of all three. For example, symptoms of Parkinson disease worsen with anxiety. The improvement noted in Parkinson disease with zolpidem use may be secondary to its anxiolytic effect through a GABAergic effect on the limbic system or elsewhere. The improvement seen in blepharospasm, catatonia, and restless legs syndrome may be caused by the benzodiazepine ω_1 receptor agonist activity of zolpidem. However, opposing this theory of purely benzodiazepine agonist mediated effects, is that parasomnias like sleepwalking are often treated with benzodiazepines like clonazepam; yet zolpidem seems to induce parasomnias in a susceptible subpopulation.

The action of zolpidem via synaptic GABA_A receptors with α_1 subunits may produce different clinical responses depending upon regional distribution of receptor subtypes. Benzodiazepines bind to all the synaptic GABA_A receptors, which are expressed throughout the nervous system. Even though zolpidem is a preferred α_1 agonist, α_1 subunits are expressed widely

throughout the CNS.¹¹ Benzodiazepine-insensitive extrasynaptic GABA_A receptors containing $\alpha_{4,6}$ subunits show much more regional specificity than benzodiazepine-sensitive synaptic GABA_A receptors containing $\alpha_{1,2,3}$, or 5.

Zolpidem has a less recognized but limited binding affinity to ω_2 benzodiazepine receptors. ω_1 and ω_2 receptors are also widely expressed throughout the human brain.¹² At higher doses these lower binding affinities may be expressed resulting in unexpected clinical outcomes. For example, anecdotally there appears to be differential efficacy of high dose zolpidem (70 mg/d) for blepharospasm, and low dose zolpidem (5-10 mg/d) for parkinsonian features. (Surprisingly at the high doses used by Garretto et. al for blepharospasm and Evidente for early onset Parkinson disease, 5 of 6 patients reported no somnolence, and only one patient had to discontinue the medication secondary to drug-induced diarrhea.^{13,14} Somnolence was overcome with slow dose titration.)

The potential clinical significance of preferred GABA_A α_1 subunit/ ω_1 receptor activation is unclear. For example, it was previously thought that zolpidem did not possess significant myorelaxant properties similar to benzodiazepines. However, anecdotal reports of efficacy for zolpidem in post-anoxic spasticity, parkinsonian dyskinesias/tremors, blepharospasm, and restless legs syndrome provides anecdotal evidence to the contrary. Zolpidem may affect many neurological diseases through binding at a variety of locations simultaneously (Figure 2). Zolpidem binding at one anatomical location is unlikely to explain all of its myriad effects. Also, electrophysiological studies suggest that different GABA subunit combinations may mediate different physiological and pharmacological properties of the ligand-operated ion channel.¹¹ Therefore, even though zolpidem has a high affinity for GABA_A receptors with the α_1 subunit, different pharmacological responses may result from different subunit combinations with the α_1 subunit. As a result, clinical efficacy in a given disease is difficult to correlate with binding and receptor activation at a single GABA_A/benzodiazepine receptor type, at a single anatomic site, or at a single dose.

An intriguing theory on the etiology of sleepwalking and SRED concerns the presence of theoretical *cerebral pattern generators* (CPGs).^{15,16} CPG are thought to be neuronal collections in the brain, brainstem or spinal cord that can potentially control innate motor behaviors essential for survival like feeding and locomotion. Diffuse zolpidem cortical binding may cause release of CPGs associated with evolutionarily conserved motor patterns such as walking and eating, leading to subsequent disorders of arousal like somnambulism and SRED. Since some CPGs may reside in the cortex, zolpidem use also release cortical patterns associated with overlearned behaviors, such as driving.

In an attempt to identify zolpidem-induced changes in cerebral glucose metabolic rates, an 18F-FDG-PET was performed in our patient on and off zolpidem. Gillin et al. compared the effects of 10 mg zolpidem and placebo on cerebral glucose metabolic rates in 12 young normal volunteers (mean age: 22.5 y) using 18F-FDG-PET.¹⁷ In that study FDG was administered about 1 h after oral administration of zolpidem while the patient was in electroencephalographically (EEG) verifiable stage 2 sleep and at a time of expected zolpidem peak concentrations (1.2 ± 0.2 h)

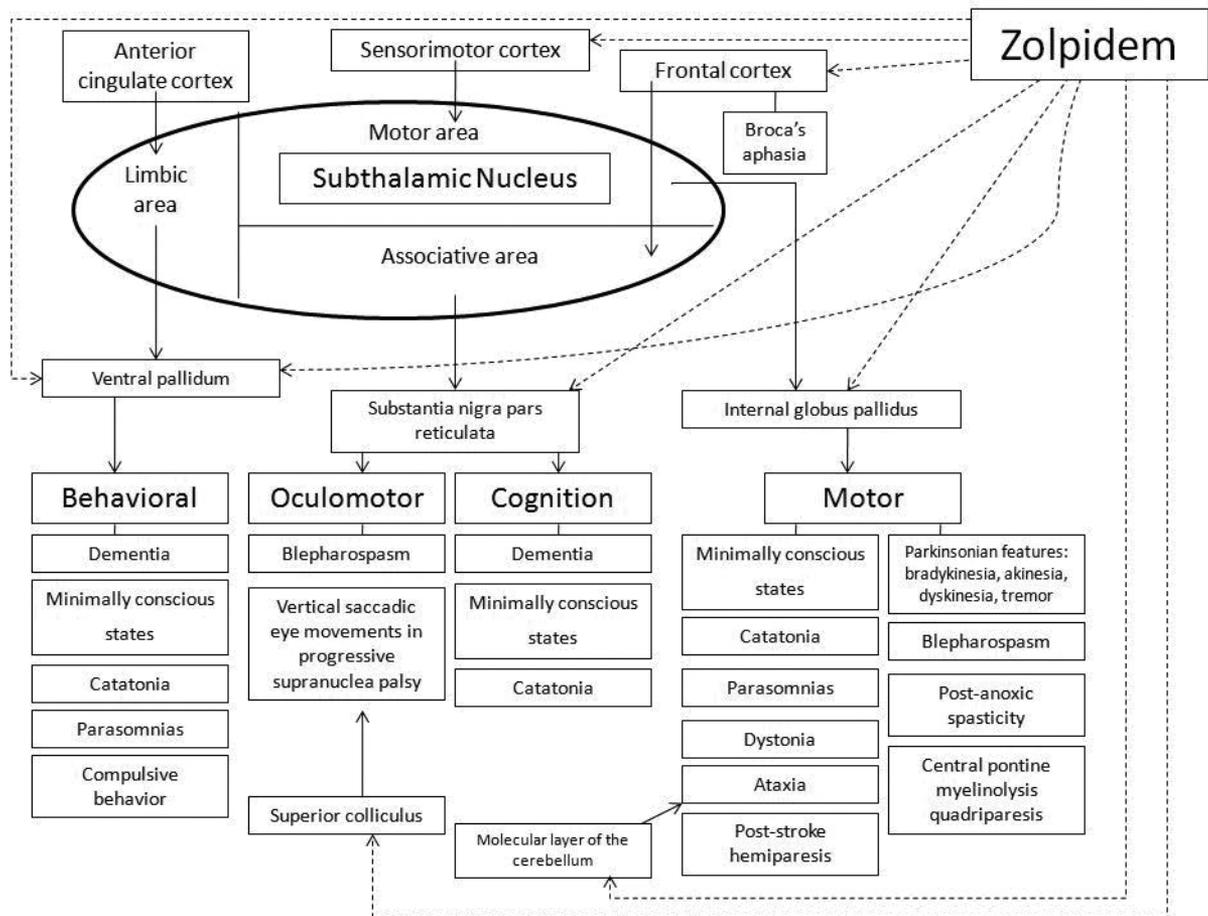


Figure 2—Regional distribution of zolpidem binding, and the potential clinical consequences. Zolpidem is a benzodiazepine receptor agonist with high binding affinity for the GABA_A (gamma-aminobutyric acid type A) receptor expressing the α_1 subunit. Benzodiazepines and benzodiazepine receptor agonists like zolpidem bind to the GABA_A receptor at sites that are distinct from the GABA binding site, thereby allosterically affecting the channel. GABA_A receptor sensitivity to benzodiazepines is mediated through α subunits. Zolpidem's action via synaptic GABA_A receptors with α_1 subunits may produce different clinical responses depending upon regional distribution of receptor subtypes. Benzodiazepines bind to all the synaptic GABA_A receptors, which are expressed throughout the nervous system. Even though zolpidem is a preferred α_1 agonist, α_1 subunits are expressed widely throughout the CNS. Given zolpidem's many binding sites, the improvement noted across a range of neurological disorders are difficult to localize to binding at a single anatomic location. GABA_A α_1 subunits/ ω_1 benzodiazepine receptors are widely distributed throughout the central nervous system, in many more areas than indicated in this simple schematic figure.

in plasma (and presumably brain). Gillin et al. found that across all cortical areas glucose metabolic rates were not significantly different on placebo versus zolpidem. Our patient's results were similar to those seen in Gillin's normal volunteers.

Compared to wake, whole brain cortical glucose metabolic rates decrease in NREM and REM stage sleep.¹⁸ One would expect a decline in cortical glucose metabolic rate with the use of sleep-inducing hypnotics like zolpidem. However, our results, along with those of Gillin show otherwise. The reasons for this are unknown.

One possible explanation may be that PET is too insensitive a tool to detect subtle localized or generalized glucose metabolic rate differences on and off zolpidem in the normal brain. If such differences could be identified, then patients who are susceptible to developing parasomnias could be identified prior to use. More importantly, this may also provide insight into other extraordinary anecdotal effects of zolpidem.

A limitation of our PET analysis was that the scan was not performed in EEG verified slow wave sleep (SWS), when para-

somnias are thought to emerge. Future 18F-FDG-PET studies in patients with zolpidem induced parasomnias could be attempted during EEG verified SWS on and off zolpidem to identify differences in glucose metabolic rates not seen in our analysis. However, this may prove to be difficult given the variable presence of SWS and the need to wait 1 h after FDG injection prior to the PET scan. By the time the patient receives the FDG injection and the scan is performed, the patient may no longer be in SWS. And though parasomnias tend to emerge in SWS, they can potentially arise from any NREM stage.

Temporal resolution is not a major limitation of PET studies in that in order to scan a brain the cortical area is divided into thirds and scanned in 3 successive 5-min sessions that are then compiled together to form an entire cortical scan. As a result, the PET findings in any particular cortical area are an estimation of glucose metabolic rate over a five minute time window. Despite this small time window, 18F-FDG-PET findings would be difficult to correlate with a particular arousal in a period of SWS. Similar studies may be performed on and off medica-

tion in NREM and REM to assess differences in brain cortical glucose metabolic rates, though the procedural limitations described above would still apply.

Single photon emission computed tomography (SPECT) studies have been used successfully to show increased cerebral blood flow in a range of cortical areas after zolpidem administration despite a more limited spatial resolution than PET. SPECT has been used to show increased regional blood flow in the frontal cortex in Broca aphasia, the cerebellum in spinocerebellar ataxia, and the contralateral hemisphere in hemiparetic patients.¹⁹⁻²¹ In normal baboon models, SPECT has been used to demonstrate that zolpidem does not cause changes in regional cerebral blood flow in normal baboons. However, in baboons with cortical injuries, zolpidem increased blood flow to the injured areas.²² Zolpidem mediated increase in regional cerebral blood flow to injured cortical areas on SPECT was attenuated by the use of flumazenil, a benzodiazepine receptor antagonist.²³ The baboon studies correlate to the case report of Brefel-Courbon et al. of a patient in a post-anoxic minimally conscious state showing arousal on clinical exam and increased cerebral glucose metabolism on 18F-FDG-PET in the bilateral post-rolandic territories and frontal lobes after zolpidem administration.²⁴ The normal baboon SPECT study findings also correlate with the 18F-FDG-PET findings in our neurologically intact patient and Gillin's normal volunteer cohort.¹⁷

To date no large scale randomized controlled trials exist assessing the efficacy of zolpidem for aphasia, blepharospasm, catatonia, central pontine myelinolysis, dementia with apraxia, Parkinson disease, progressive supranuclear palsy, restless legs syndrome, post-anoxic spasticity, or spinocerebellar ataxia. The clinical benefit of zolpidem for patients in minimally conscious states is currently being explored in clinical trials.²⁵ These results may also help to further understand sleep-wake mechanisms and the function of hypnotics.

The anecdotal benefits of zolpidem have provided hope that damage to brain tissue after strokes anoxic insults previously thought to be permanent may actually be reversible. Zolpidem may reactivate cortical areas that have undergone injury-induced dormancy, or there may be more redundancy built into our brains than previously believed, e.g. CPGs. GABAergic hypnotics like zolpidem through diffuse cortical binding may somehow unmask this redundancy.

Future studies may also shed light on whether different susceptibilities to zolpidem induced parasomnias and its other effects may depend upon the formulation used. For example, Chiang et al. reported 2 patients who experienced zolpidem induced sleepwalking and SRED on only the extended release formulation and not the non-extended release formulation.²⁶ Validation of these anecdotal findings and investigations into the new sublingual formulation of zolpidem may provide insight into how formulation dependent pharmacokinetics may influence an individual's susceptibility to zolpidem-induced parasomnias.²⁷

Investigations into the mechanisms of action of GABAergic induced parasomnias may overturn therapeutic nihilism for a variety of neurological disease. Capitalizing upon zolpidem's myriad anecdotal serendipitous effects, basic science research using animal models of non-sleep-wake related neurological disorders may provide us with a of understanding how the brain reorganizes itself after injury. Also genetic analysis of individu-

al patients may also provide insight into potentially identifiable pharmacogenetic vulnerabilities/susceptibilities. These exciting and unexplored avenues of research may be used in the treatment of disease previously thought untreatable.

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DISCLOSURE STATEMENT

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REFERENCES

1. American Academy of Sleep Medicine. The international classification of sleep disorders: diagnostic & coding manual. 2nd ed. Westchester, IL: American Academy of Sleep Medicine, 2005.
2. National Institutes of Health State of the Science Conference statement on Manifestations and Management of Chronic Insomnia in Adults, June 13-15, 2005. *Sleep* 2005;28:1049-57.
3. Ganzoni E, Santoni JP, Chevillard V, Sebillle M, Mathy B. Zolpidem in insomnia: a 3-year post-marketing surveillance study in Switzerland. *J Int Med Res* 1995;23:61-73.
4. Sauvanet JP, Maarek L, Roger M, Renaudin J, Louvel E, Orofi-amma B. Open long-term trials with zolpidem in insomnia. In: Sauvanet JP, Langer SZ, Morselli PL, eds. *Imidazopyridines in sleep disorders*. New York: Raven Press, 1988:339-49.
5. Roehrs T, Vogel G, Vogel F, et al. Eligibility requirements in hypnotic trials. *Sleep* 1985;8:34-9.
6. Harrison NL. Mechanisms of sleep induction by GABA(A) receptor agonists. *The J Clin Psychiatry* 2007;68(Suppl 5):6-12.
7. Holm KJ, Goa KL. Zolpidem: an update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. *Drugs* 2000;59:865-89.
8. Langer SZ, Arbilla S, Scatton B, Niddam R, Dubois A. Receptors involved in the mechanism of action of zolpidem. In: Sauvanet JP, Langer SZ, Morselli PL, eds. *Imidazopyridines in sleep disorders*. New York: Raven Press, 1988:55-69.
9. Canaday BR. Amnesia possibly associated with zolpidem administration. *Pharmacotherapy* 1996;16:687-9.
10. Collis R. Hotels wake up to sleepwalking clients. 2007 [cited 2007 June 13, 2008]; Available from: <http://www.iht.com/articles/2007/11/15/travel/trfreq16.php>
11. Pirker S, Schwarzer C, Wiesenthaler A, Sieghart W, Sperk G. GABA(A) receptors: immunocytochemical distribution of 13 subunits in the adult rat brain. *Neuroscience* 2000;101:815-50.
12. Dennis T, Dubois A, Benavides J, Scatton B. Distribution of central omega 1 (benzodiazepine1) and omega 2 (benzodiazepine2) receptor subtypes in the monkey and human brain. An autoradiographic study with [3H]flunitrazepam and the omega 1 selective ligand [3H]zolpidem. *J Pharmacol Exp Ther* 1988;247:309-22.
13. Garretto NS, Bueri JA, Rey RD, Arakaki T, Nano GV, Mancuso M. Improvement of blepharospasm with Zolpidem. *Mov Disord* 2004;19:967-8.
14. Evidente VG. Zolpidem improves dystonia in "Lubag" or X-linked dystonia-parkinsonism syndrome. *Neurology* 2002;58:662-3.

15. Tassinari CA, Rubboli G, Gardella E, et al. Central pattern generators for a common semiology in fronto-limbic seizures and in parasomnias. A neuroethologic approach. *Neurol Sci* 2005;26 Suppl 3:s225-32.
16. Yuste R, MacLean JN, Smith J, Lansner A. The cortex as a central pattern generator. *Nature Rev* 2005;6:477-83.
17. Gillin JC, Buchsbaum MS, Valladares-Neto DC, et al. Effects of zolpidem on local cerebral glucose metabolism during non-REM sleep in normal volunteers: a positron emission tomography study. *Neuropsychopharmacology* 1996;15:302-13.
18. Buchsbaum MS, Hazlett EA, Wu J, Bunney WE Jr. Positron emission tomography with deoxyglucose-F18 imaging of sleep. *Neuropsychopharmacology* 2001;25(5 Suppl):S50-6.
19. Cohen L, Chaaban B, Habert MO. Transient improvement of aphasia with zolpidem. *New Engl J Med* 2004;350:949-50.
20. Clauss RP, Nel WH. Effect of zolpidem on brain injury and dischisis as detected by 99mTc HMPAO brain SPECT in humans. *Arzneimittelforschung* 2004;54:641-6.
21. Clauss R, Satheke M, Nel W. Transient improvement of spinocerebellar ataxia with zolpidem. *New Engl J Med* 2004;351:511-2.
22. Clauss RP, Dormehl IC, Oliver DW, Nel WH, Kilian E, Louw WK. Measurement of cerebral perfusion after zolpidem administration in the baboon model. *Arzneimittelforschung* 2001;51:619-22.
23. Clauss RP, Dormehl IC, Kilian E, Louw WK, Nel WH, Oliver DW. Cerebral blood perfusion after treatment with zolpidem and flumazenil in the baboon. *Arzneimittelforschung* 2002;52:740-4.
24. Brefel-Courbon C, Payoux P, Ory F, et al. Clinical and imaging evidence of zolpidem effect in hypoxic encephalopathy. *Ann Neurol* 2007;62:102-5.
25. May 2008 [cited; Available from: www.regentherapeutics.com
26. Chiang A, Krystal A. Report of two cases where sleep related eating behavior occurred with the extended-release formulation but not the immediate-release formulation of a sedative-hypnotic agent. *J Clin Sleep Med* 2008;4:155-6.
27. Roth T, Krystal AD, Maguire Y, Singh N, Maytom M. Pharmacokinetics of the sublingual zolpidem tartrate 3.5 mg lozenge compared to the oral zolpidem tartrate 10 mg tablet. *Sleep* 2008;31(Abtract Supplement):A235.
28. Thomas P, Rasclé C, Mastain B, Maron M, Vaiva G. Test for catatonia with zolpidem. *Lancet* 1997;349:702.
29. Wang WT, Chen YY, Wu SL, Wei TS, Liu SY. Zolpidem dramatically improved motor and speech function in a patient with central pontine myelinolysis. *Eur J Neurol* 2007;14:e9-10.
30. Tsai MJ, Tsai YH, Huang YB. Compulsive activity and anterograde amnesia after zolpidem use. *Clin Toxicol (Philadelphia, PA)* 2007;45:179-81.
31. Jarry C, Fontenas JP, Jonville-Bera AP, Autret-Leca E. Beneficial effect of zolpidem for dementia. *Ann Pharmacother* 2002;36:1808.
32. Clauss RP, Guldenpfennig WM, Nel HW, Satheke MM, Venkanagari RR. Extraordinary arousal from semi-comatose state on zolpidem. A case report. *S Afr Med J* 2000;90:68-72.
33. Clauss R, Nel W. Drug induced arousal from the permanent vegetative state. *NeuroRehabilitation* 2006;21:23-8.
34. Cohen SI, Duong TT. Increased arousal in a patient with anoxic brain injury after administration of zolpidem. *Am J Phys Med Rehabil* 2008;87:229-31.
35. Shames JL, Ring H. Transient reversal of anoxic brain injury-related minimally conscious state after zolpidem administration: a case report. *Arch Phys Med Rehabil* 2008;89:386-8.
36. Daniele A, Albanese A, Gainotti G, Gregori B, Bartolomeo P. Zolpidem in Parkinson's disease. *Lancet* 1997;349:1222-3.
37. Ruzicka E, Roth J, Jech R, Busek P. Subhypnotic doses of zolpidem oppose dopaminergic-induced dyskinesia in Parkinson's disease. *Mov Disord* 2000;15:734-5.
38. Farver DK, Khan MH. Zolpidem for antipsychotic-induced parkinsonism. *Ann Pharmacother* 2001;35:435-7.
39. Daniele A, Moro E, Bentivoglio AR. Zolpidem in progressive supranuclear palsy. *New Engl J Med* 1999;341:543-4.
40. Mayr BJ, Bonelli RM, Niederwieser G, Koltringer P, Reisecker F. Zolpidem in progressive supranuclear palsy. *Eur J Neurol* 2002;9:184-5.
41. Gericke CA, Ludolph AC. Chronic abuse of zolpidem. *JAMA* 1994;272:1721-2.
42. Bezerra ML, Martinez JV. Zolpidem in restless legs syndrome. *Eur Neurol* 2002;48:180-1.
43. Mendelson WB. Sleepwalking associated with zolpidem. *J Clin Psychopharmacol* 1994;14:150.
44. Harazin J, Berigan TR. Zolpidem tartrate and somnambulism. *Mil Med* 1999;164:669-70.
45. Morgenthaler TI, Silber MH. Amnesic sleep-related eating disorder associated with zolpidem. *Sleep Med* 2002;3:323-7.
46. Sattar SP, Ramaswamy S, Bhatia SC, Petty F. Somnambulism due to probable interaction of valproic acid and zolpidem. *Ann Pharmacother* 2003;37:1429-33.
47. Sharma A, Dewan VK. A case report of zolpidem-induced somnambulism. Primary care companion to *J Clin Psychiatry* 2005;7:74.
48. Najjar M. Zolpidem and amnesic sleep related eating disorder. *J Clin Sleep Med* 2007;3:637-8.
49. Sansone RA, Sansone LA. Zolpidem, somnambulism, and nocturnal eating. *Gen Hosp Psychiatry* 2008;30:90-1.
50. Shadan FF, Poceta JS, Kline LE. Zolpidem for postanoxic spasticity. *South Med J* 2004;97:791-2.

Table S1—Zolpidem: A Spectrum of Unintended Effects and Potential Uses. SRED: sleep-related eating disorder.

Reference	Age, sex, and clinical state	Dose	Description of response
Aphasia			
Cohen et al. 2004 ¹⁹	52, female, stroke of left insula, putamen, and superior temporal gyrus with resultant Broca aphasia	Zolpidem 10 mg once/d Time to response: 20 minutes Duration of response: unknown	Patient regained effective speech, naming, and repetition.
Blepharospasm, Meige syndrome (oromandibular dystonia and blepharospasm)			
Garretto et al. 2004 ¹³	Three patients Patient 1: 57, woman, Meige syndrome Patient 2: 63, male, blepharospasm Patient 3: 66, male, Meige syndrome	Patient 1: Zolpidem 10 mg every 2-3 h (70 mg/d) Time to response: 30 min Duration of response: 3 h Patient 2: Zolpidem 10 mg 3 times/d Time to response: 20-30 min Duration of response: 3 h Patient 3: Zolpidem 10 mg twice a day Time to response: 30 min Duration of response: 3 h	Blepharospasm improved in all 3. Effect on oromandibular dystonia in the 2 patients with Meige syndrome was not mentioned.
Catatonia			
Thomas et al. 1997 ²⁸	21, woman, schizoaffective disorder. One month after discontinuation of haloperidol, patient developed severe oppositional behavior, mutism, staring, posturing, and refusal of food.	Zolpidem 10 mg once/d Time to response: 15 min Duration of response: 4 h	All behavior and motor symptoms resolved on zolpidem.
Central pontine myelinolysis			
Wang et al. 2007 ²⁹	51, female, post-surgical complication resulting in central pontine myelinolysis with spastic quadriparesis and pseudobulbar palsy	Zolpidem 10 mg once/d Time to response: 20 min Duration of response: 4 h	Regained facial expression, effective speech, and smooth limb movements
Compulsive behavior while awake			
Tsia et al. 2007 ³⁰	Three previously healthy patients Patient 1: 34, female Patient 2: 40, female Patient 3: 50, female	Zolpidem 10 mg once/d All 3 patients exhibited compulsive behaviors (cleaning, shopping, and eating) with anterograde amnesia for the events.	Events were not considered to be sleepwalking because patients were able to communicate fluently and perform normally beyond the compulsive activity. Events stopped with cessation of zolpidem in all 3 patients.
Dementia with apraxia			
Jarry et al. 2002 ³¹	60, woman, alcoholic, reduced cognition, memory loss, apraxia, inability to join in conversation	Zolpidem 10 mg once/d Time to response: 45-60 min Duration of response: 3 h	Improvement in cognition and praxis. Regained the ability to perform simple chores around the home.
Minimally conscious states			
Claus et al. 2000 ³²	28, male, motor vehicle accident resulting in post-anoxic minimally conscious state	Zolpidem 10 mg once/d, Time to response: 15 min Duration of response not explicitly stated	Interacted spontaneously and responded to simple questions with short appropriate answers

Reference	Age, sex, and clinical state	Dose	Description of response
Claus et al. 2006 ³³	Three patients: Patient L: 31, male, Patient N: 31, male, Patient G: 29, male. All 3 had motor vehicle accidents resulting in post-anoxic minimally conscious state	Doses unknown. Time to response: L: 20-30 min, N: 1 h; G: 20-30 min. Duration of response was 4 h for all 3 patients.	L: meaningful interactions/ conversations with caregivers, purposeful response to stimuli, voluntary behavior. N: Cessation of random screaming episodes. Watched television and laughed at funny scenes. Stated his name and age. G: Meaningful interactions with caregivers. Lifted hands, counted to 5, and smiled on command.
Brefel-Courbon et al. 2007 ²⁴	48, male, suicide attempt by hanging resulting in post-anoxic encephalopathy with minimally conscious state	Zolpidem 10 mg once/d Time to response: 20 min Duration of response: 2-3 h	Increased arousal; communicated with family; swallowed food; moved spontaneously in bed
Cohen et al. 2008 ³⁴	35, male, cardiac arrest resulting in post-anoxic encephalopathy with minimally conscious state	Zolpidem 5 mg once a day → 10 mg in the morning and 5 mg in the evening → 10 mg twice/d, Time to response: 1 h Duration of response: 3-6 h depending on dosing	Zolpidem 5 mg once a day: Increased arousal and more interactive with caregivers. Could toss a football Zolpidem 10 mg/ 5 mg: Walked with assistance Zolpidem 10 mg/ 10 mg: Spoke more frequently and fluently. Walked unassisted.
Shames et al. 2008 ³⁵	50, woman, cardiac arrest resulting in post-anoxic encephalopathy with minimally conscious state	Zolpidem 10 mg once/d Time to response: 30 min Duration of response: 3 h	Increased arousal. Alert and oriented to self and place. Cessation of athetoid movements. Regained full voluntary movements of all 4 extremities.
Parkinson disease, Parkinsonian features			
Daniele et al. 1997 ³⁶	10 patients, mean age 69.9	Zolpidem 10 mg once/d In the responders (6/10 patients): Time to response: 45-60 min Duration of response: 2-4 h	6/10 patients showed motor improvement in facial expression, rigidity, akinesia, bradykinesia, posture and gait
Ruzicka et al. 2000 ³⁷	45, female, Parkinson disease with generalized choreic dyskinesia post-levodopa administration	Zolpidem 5 mg per day Time to response: 30 min Duration of response: 2 h	Limb and trunk dyskinesia ceased on zolpidem
Farver et al. 2001 ³⁸	31, male, schizoaffective disorder, illicit substance abuse (cocaine, amphetamines, marijuana) Patient developed parkinsonian rest tremor on antipsychotic medications. Tremor failed to respond to lowering the antipsychotic dose, adding anticholinergic or dopaminergic medications, or switching to novel antipsychotics.	Zolpidem 5 mg 4 times/d	The patient's tremors resolved within 1 month of zolpidem. With withdrawal of zolpidem the tremors returned. They ceased once again when zolpidem was restarted.

Reference	Age, sex, and clinical state	Dose	Description of response
Evidente 2002 ¹⁴	Three patients with X-linked early onset parkinsonism with dystonia (Lubag syndrome) Patient 1: 41, male Patient 2: 38, male Patient 3: 36, male	Patient 1: Zolpidem 10 mg every 2 h Time to response: 15 min Duration of response: 2 h Patient 2: Zolpidem 10 mg twice/d Time to response: 40 min Duration of response: 3 h Patient 3: Zolpidem 10 mg twice/d Time to response: 45 min Duration of response: 2 h	All three patients had improvement in dystonia and parkinsonism on zolpidem
Progressive supranuclear palsy (PSP)			
Daniele et al. 1999 ³⁹	10 patients with PSP, mean age: unknown	Crossover trial: All patients received zolpidem 5 mg once a day, zolpidem 10 mg once a day, levodopa-carbidopa 250 mg-25 mg, and placebo. Time to response to zolpidem: 40-60 min Duration of response to zolpidem: 2 h	Zolpidem, unlike levodopa-carbidopa or placebo, improved saccadic eye movements in 4/10 patients on Zolpidem 10 mg/d
Mayr et al. 2002 ⁴⁰	61, male	Zolpidem 5 mg/d Time to response and duration of response: unknown	Patient showed improvement in vertical gaze palsy and parkinsonism. Patient showed response for 4 weeks. Second trial of zolpidem 2 months later showed no benefit.
Psychostimulant effect			
Gericke et al. 1994 ⁴¹	33, male, depression	Zolpidem 80 mg/d. Patient self-increased the dose from 10 mg per day due to insomnia and accidentally discovered a stimulant effect at higher doses with improvement in depression. Time to stimulant response: 20 min Duration of response: 5-6 h	Generalized tonic-clonic seizure occurred at 80 mg per day.
Restless legs syndrome			
Bezerra et al. 2002 ⁴²	8 patients, 3 male, Mean age: 50.8	Zolpidem 10 mg once/d Time to response: mean of 4 days Continued response on medication with no relapses	Positive response was noted in all patients, regardless of age and severity of restless legs syndrome
Sleepwalking with or without sleep related eating disorder (SRED)			
Sauvanet et al. 1988 ⁴	Post-marketing study showed 1 of 96 patients developed sleepwalking on zolpidem	Dose unknown	Data not available
Mendelson 1994 ⁴³	20, male, participant in clinical study of nocturnal effects of sedative medications History of sleepwalking as a child.	Zolpidem 10 mg at bedtime before polysomnogram.	Investigator initiated auditory tone aroused patient out of stage 4 sleep. Patient stood up and walked on the bed. He was confused when sleep technician entered room and asked him to sit. He had vague memory of the events
Ganzoni et al. 1999 ³	Post-marketing study showed 7 of 1972 patients developed sleepwalking on zolpidem	Dose unknown	Data not available

Reference	Age, sex, and clinical state	Dose	Description of response
Harazin et al. 1999 ⁴⁴	46, male, shift work related insomnia Negative history for sleepwalking	Zolpidem 10 mg at bedtime	Within 4 days of initiation of zolpidem he would arise at night to prepare a meal and eat it. He had no memory of the events. Medication was discontinued. Unknown whether events recurred off zolpidem.
Morgenthaler, et. al. 2002 ⁴⁵	Five patients Mean age: 61.4, 3 male All 5 patients had restless legs syndrome, 3 had obstructive sleep apnea All 5 patients had a negative history for sleepwalking	Zolpidem 10-20 mg once/d	All exhibited sleepwalking and SRED 4/5 had vague memory of the events. Events ceased in all patients with zolpidem discontinuation
Sattar et al. 2003 ⁴⁶	47, male, bipolar disorder. Negative history for sleepwalking.	Citalopram 40 mg once/d, valproic acid 250 mg twice/d, Zolpidem 5 mg at bedtime	Sleepwalking started when valproic acid was added to citalopram and zolpidem. He had no memory of the events. Events ceased when valproic acid was withdrawn and returned when valproic acid was restarted.
Sharma et al. 2005 ⁴⁷	19, male, schizoaffective disorder Negative history for sleepwalking	Zolpidem 10 mg at bedtime	Within a few days of initiation of zolpidem he started to sleepwalk and talk incoherently. He had no memory of the events. Events ceased with zolpidem discontinuation.
Najjar 2007 ⁴⁸	46, female, depression, obstructive sleep apnea on continuous positive airway pressure therapy Negative history for sleepwalking or parasomnias	Zolpidem extended-release form 6.25 mg once/d	Sleepwalking and SRED began immediately after initiation of zolpidem use and ceased immediately after it was discontinued.
Chiang et al. 2008 ²⁶	Two patients: Patient 1: 75, female Patient 2: 70, female Both patients had restless legs syndrome, obstructive sleep apnea, and used continuous positive airway pressure therapy Both patients had a negative history for sleepwalking or SRED	Both patients had sleepwalking and SRED on zolpidem extended release 12.5 mg once/d. Neither patient experienced sleepwalking or SRED on the immediate release form of zolpidem.	Both patients experienced sleepwalking and SRED immediately after initiation of extended release zolpidem use and ceased immediately after it was discontinued
Sansone et al. 2008 ⁴⁹	51, female,	Zolpidem 10 mg at bedtime	Arose at night to prepare a meal and eat it. She had no memory of the events. Events stopped with cessation of zolpidem.
Post-anoxic spasticity			
Shadan et al. 2004 ⁵⁰	28, male, cardiac arrest resulting in post-anoxic spasticity	Zolpidem 10 mg once a day Time to response: 20 min Duration of response: 2-4 h	Decrease in muscle rigidity, spasticity and dystonic posturing
Spinocerebellar ataxia			
Claus et al. 2004 ²¹	5 members of a family, 3 male, Mean age: 33	Zolpidem 10 mg once/d Time to response: 1 h Duration of response: unknown	4/5 patients showed improvement of ataxia with zolpidem



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Insomnia in United States Military Veterans: An Integrated Theoretical Model

Jaime M. Hughes^a, Christi S. Ulmer^{a,b}, Jennifer M. Gierisch^{a,c}, S. Nicole Hastings^{a,d,e}, and Matthew O. Howard^f

^aHealth Services Research & Development, Durham VA Health Care System, Durham, NC

^bDepartment of Psychiatry and Behavioral Sciences, Duke University, Durham, NC

^cDepartment of General Internal Medicine, Duke University, Durham, NC

^dGeriatric Research, Education, and Clinical Center, Durham VA Health Care System, Durham, NC

^eDepartment of Medicine and Center for the Study of Aging and Human Development, Duke University, Durham, NC

^fSchool of Social Work, University of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract

Marked by difficulty falling or staying asleep and/or poor sleep leading to daytime dysfunction, insomnia contributes to functional impairment, poor health, and increased healthcare utilization when left untreated. As many as two-thirds of Iraq and Afghanistan military veterans complain of insomnia. Older veterans of prior conflicts report insomnia occurring since initial service, suggesting a chronic nature to insomnia in this population. Despite insomnia's high prevalence and severe consequences, there is no theoretical model to explain either the onset or chronicity of insomnia in this growing patient population. Existing theories view insomnia as an acute, unidirectional phenomenon and do little to elucidate long-term consequences of such problems. Existing theories also fail to address mechanisms by which acute insomnia becomes chronic. This paper presents an original, integrated theoretical model that draws upon constructs from several prominent behavioral medicine theories to reconceptualize insomnia as a chronic, cyclical problem

Corresponding Author: Jaime M. Hughes, PhD, MPH, MSW, Health Services Research & Development, Durham VA Health Care System, 508 Fulton Street (152), Durham, NC 27705, Phone: (919) 286 – 0411, x4042, jane.hughes@va.gov.

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Contributors

Dr. Hughes developed the first draft of the conceptual model and wrote the first draft of the manuscript. Drs. Ulmer, Gierisch, Hastings, and Howard served as theoretical consultants during the development of the conceptual model and assisted with review and editing of the final manuscript. All authors have contributed to and have approved the final manuscript.

Conflict of Interest

The authors have no conflicts of interest to disclose.

that is both a consequence and predictor of stress. Additional research examining the relationships between stress, sleep, resilience, and outcomes of interest could inform clinical and research practices. Addressing sleep problems early could potentially enhance adaptive capacity, thereby reducing the risk for subsequent negative outcomes.

Keywords

insomnia; sleep; stress; coping; resilience; veterans

Sleep is a basic biological need responsible for a range of restorative functions including emotion regulation and memory consolidation, muscle and tissue repair, and stress hormone regulation (Dement & Vaughan, 1999). Despite its necessity, sleep is often ignored as a core health behavior, rarely addressed within biopsychosocial assessments or routine primary care visits, and generally not integrated into chronic disease management programs. Sleep problems are particularly common among United States military veterans, with one-half to two-thirds of the 2.5 million U.S. military troops who served in Afghanistan (Operation Enduring Freedom, OEF) and Iraq (Operation Iraqi Freedom, OIF) complain of insomnia problems on returning home (Amin, Parisi, Gold, & Gold, 2010; Seelig et al., 2011). Insomnia complaints are also prevalent among veterans of earlier wars, including Vietnam and Korea conflicts. Additionally, many of these older veterans report that sleep problems initially began during or immediately following their military service and have persisted in the decades since separating from the military (Hughes & Martin, 2015; Ryden et al., 2015).

These findings suggest insomnia problems are chronic within veteran populations; yet, a lack of longitudinal data prohibits researchers from identifying mechanisms that contribute to such chronicity and from understanding how such problems change over a veteran's life course. Given sleep problems are tied to a number of negative physical and psychological outcomes (Fernandez-Mendoza & Vgontzas, 2013), it is critical that researchers and clinicians develop a better understanding of this growing problem. The overarching goal of this paper is to offer a theoretical model of insomnia in the veteran population. Although this model can be applied to veterans of all ages and military cohorts, a major goal of the model is to place insomnia-like sleep problems of returning OEF/OIF veterans into a larger, lifespan context as a means of advocating for additional research on the role sleep problems may play in longterm health and aging. While military-specific stressors will be addressed, we believe that elements of this integrated model can be applied to other patient populations, including those who have experienced significant stress or trauma.

Insomnia in Military Veterans

Chronic Insomnia Disorder is a common behavioral sleep disorder clinically defined as dissatisfaction with sleep quantity or quality marked by complaints of difficulty falling or staying asleep, waking up earlier than desired, or sleep that is non-restorative and the cause of significant daytime impairment. Such problems are not related to other medical or sleep disorders, exist despite adequate opportunity and environment for sleep, and are endorsed three or more nights per week for three months or longer (American Psychiatric Association, 2013). Insomnia and/or insomnia-like symptoms are present in 27–54% of military

personnel and veterans (Hoge, W. et al., 2008; Mysliwec, McGraw, Smith, Trapp, & Roth, 2013), rates that are two to three times higher than in the general U.S. adult population (Ford, Cunningham, Giles, & Croft, 2015; Roth, 2007). The rate of incident insomnia cases in military personnel saw a 19-fold increase from 2000 to 2009 (Mysliwec et al., 2013). The prevalence of insomnia among Veterans Health Administration (VHA) users is expected to continue to rise as many troops who served after September 11, 2001 continue to retire from military service and begin accessing VHA healthcare in the coming years (Campbell, Shattuck, Germain, & Mysliwec, 2015).

Risk Factors

Both modifiable and non-modifiable risk factors contribute to insomnia. This paper addresses the role of stress regulation and coping in sleep problems with a behavioral etiology. Insomnia-like sleep problems may be a function of an individual's stress response whereby poor sleep is a function of inadequate coping and/or poor regulation of stress across physiological, cognitive, and/or emotional processes. In this context, stress refers to any event or stimulus that causes a disruption in balance, or homeostasis. Laboratory studies indicate that higher baseline levels of stress reactivity are associated with insomnia and predict future cases of the disorder (Drake, Friedman, Wright, & Roth, 2011; Drake, Richardson, Roerhs, Scofield, & Roth, 2004). In addition, individuals with insomnia have been shown to report experiencing more daily stressors and negatively evaluating such stressors (Morin & Ivers, 2003).

Initial military involvement, including enlistment and basic training, present a range of different stressors and often trigger sleep disturbance due to irregular schedules and ongoing physical, social, and emotional demands (Peterson, Goodie, Satterfield, & Brim, 2008). Deployment to a war region typically requires several days of laborious travel and crossing of multiple time zones that can disrupt one's natural circadian rhythm, or sleep schedule, and trigger sleep difficulties (Troxel et al., 2015). Deployment typically involves irregular work schedules, overnight watch demands, exposure to warzone and combat-related stressors, and risk of physical and psychological injury, including traumatic brain injury. While no research has formally documented the cause, or trajectory, of insomnia in military personnel, it is likely that one or more of the aforementioned factors served as an initial trigger of insomnia symptoms.

Recent research has focused on sleep problems among active duty military personnel, including increasing rates of incident insomnia and sleep apnea diagnoses (Mysliwec et al., 2013), heightened mental health risks associated with insomnia symptoms (Gehrman et al., 2013), and the link between sleep and impaired work performance (Seelig et al., 2016; Troxel et al., 2015). Less research has focused on sleep after military retirement. Stressors related to military separation, or retirement, and reintegration into civilian life can also trigger insomnia (Bramoweth & Germain, 2013). Additionally, many service members experience an inability to return to a "normal" sleep schedule after experiencing short sleep duration or irregular schedules while deployed (Castro, Kintzle, & Hassan, 2015; Haynes, Parthasarathy, Bootzin, & Krakow, 2013). Additional reintegration-related stressors include readjustment to family and social circles, securing civilian employment, maintaining

financial stability, and living with the physical and psychiatric comorbidities caused by deployment or combat-related stressors. These stressors can cause difficulty falling or staying asleep, or sleep that is restless and disturbed, thereby creating new sleep problems or exacerbating existing problems that began prior to or during deployment.

Consequences of Insomnia

Persistent insomnia can lead to poor health outcomes and chronic conditions (Fernandez-Mendoza & Vgontzas, 2013; Taylor et al., 2007), exacerbate symptoms of traumatic brain injury (Macera, Aralis, Rauch, & MacGregor, 2013), reduce overall quality-of-life (Katz & McHorney, 2002), and increase risk for morbidity and premature mortality (Dew et al., 2003; Kripke, Garfinkel, Wingard, Klauber, & Marler, 2002). Chronic sleep problems can also negatively impact day-to-day outcomes including task performance (Pilcher & Huffcutt, 1996), stress coping (Hamilton, Delwyn, & Karlson, 2007), and management of chronic health conditions (Ahn, Jiang, Smith, & Ory, 2014).

Function, Performance and Health Management—Chronic insomnia impairs function and performance across cognitive, emotional, social, and physical domains (Killgore, Balkin, & Westensten, 2006; Killgore et al., 2008; Pilcher & Huffcutt, 1996). Adequate functioning in these areas enables veterans to adapt to and cope with daily hassles and reintegration stressors noted earlier. However, impairments in one or more domains can reduce ability to cope with acute and ongoing stressors. As a result, functional performance and independence decline, thereby decreasing the likelihood of successful reintegration into civilian life (Institute of Medicine, 2013; Pilcher & Huffcutt, 1996).

Many of these aforementioned impairments can also reduce a veteran's capacity to cope with health-related stressors, a concept of particular interest to clinicians and health services researchers within the VHA. Medically complex patients, defined as individuals with two or more chronic conditions, who are challenged by managing such conditions (Shippee, Shah, May, Mair, & Montori, 2012), represent a growing subgroup of veterans utilizing VHA healthcare (Yoon, Schott, Phibbs, & Wagner, 2011; Yu et al., 2003). Medical complexity is often marked by a cycle of ongoing acute and chronic health-related stressors. Patients cycle through these stressors and strive to achieve and maintain a balance between workload demands (i.e. management of chronic diseases) and physical and psychological resources (Zullig et al., 2016). Successful balance and management of stressors is bolstered by high physical and psychological reserve and capacity (Zullig et al., 2016). These new models of complexity support the idea that capacity is malleable and can be impacted by resources, behaviors, and events on individual and community levels. Although sleep problems, including insomnia, are gaining more attention within the VHA, sleep patterns and behaviors are not explicitly addressed in these models.

Mental Health—Insomnia symptoms are common among veterans with mental health disorders. In one study, more than three-quarters reported difficulty falling or staying asleep and just over one-half reported being at least moderately distressed about sleep that was restless or disturbed (Ulmer et al., 2015). Although this research sample was designed to over-recruit veterans with mental health symptoms, this same study drew attention to the

notably high prevalence of sleep difficulties in veterans without a mental health diagnosis, including approximately seventy percent who met clinical criteria for poor sleep quality, defined as a score of five or greater on the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989).

The high rate of sleep problems among veterans without mental health diagnoses is alarming given that research with veteran and non-veteran populations has found that chronic sleep problems predict incident mental health diagnoses (Baglioni et al., 2011; Breslau, Roth, Rosenthal, & Andreski, 1996; D. Ford & Kamerow, 1989; Perlis et al., 2006) and suicidal ideation (Pigeon, Britton, Ilgen, Chapman, & Conner, 2013; Pigeon, Pinquart, & Connor, 2012) as well as persistence of existing mental health problems, including depression (Pigeon, Unutzer, & Perlis, 2008), and increased risk for readmission to a partial hospitalization psychiatry program (Koffel, Thuras, Chakravorty, Germain, & Khawakaja, 2015). In a large study of OEF/OIF service members, researchers found that military personnel with predeployment insomnia symptoms had greater odds of developing depression, anxiety, and PTSD at follow-up (Gehrman et al., 2013). Another longitudinal study found that insomnia measured at four months post-deployment was a significant predictor of depression and PTSD at 12-months post-deployment (Wright et al., 2011).

While it is too early to examine the long-term effects of military service on OEF/OIF service members' health, a great deal can be learned from studying the aging trajectories of veterans from earlier conflicts, including the Vietnam War. By better understanding how early or mid-life military service contributed to long-term outcomes in these cohorts, researchers and clinicians can develop new practices that can be translated into more effective and preventive-oriented care for veterans of more recent conflicts (Marmar, 2009). For example, nearly 40 years after the conclusion of the Vietnam War, Marmar and colleagues (2015) noted that lifetime and current diagnoses of PTSD and major depression were prevalent among veterans.

PTSD has been linked to increased healthcare utilization and costs in veterans of recent and earlier war conflicts (E. Hoge, Austin, & Pollack, 2007; Schnurr, Spiro III, & Paris, 2000). A growing line of research suggests that some veterans involved in earlier war conflicts experience premature functional decline and accelerated aging (Lohr et al., 2015; Wolf et al., 2016) as a result of service-related experiences and injuries, including PTSD. Much of this research points to the detrimental effects of PTSD, yet little research has isolated mechanisms that link early or mid-life military experiences to PTSD and subsequent decline. While sleep problems were not measured directly in the aforementioned studies, sleep problems are a core component of PTSD diagnostic criteria (American Psychiatric Association, 2013). Given this common symptom pattern, it is possible that untreated sleep problems of Vietnam Era veterans partially contributed to mid- or late-life PTSD. However, the lack of longitudinal data and absence of sleep questionnaires in this data prevent this hypothesis from being confirmed. The model presented here illustrates one potential pathway through which early life trauma and insomnia problems may impact mid- or late-life physical and mental health.

Insomnia and Resilience as Missing Links between Military Service and Poor Outcomes

Insomnia problems contribute to negative health outcomes and can become chronic, surfacing repeatedly over one's life course. However, mechanisms contributing to this chronicity have not been identified. The mechanisms linking sleep problems, including insomnia, to new mental health diagnoses remain unclear. However, one hypothesized explanation is that chronic poor sleep reduces one's coping abilities. As a result, when subsequent stressors do arise, individuals with sleep problems respond with reduced coping abilities (Gehrman et al., 2013). A reduced capacity to positively cope with stress may lead to a more negative stress outcome, such as PTSD (Benight & Bandura, 2004).

Researchers studying active duty military and veteran populations have a growing interest in resilience and its role in everything from operational readiness during deployment period to mental health and readjustment in the post-deployment period (Seelig et al., 2016; Stanley, Schaldach, Kiyonga, & Jha, 2011; Troxel et al., 2015; Young-McCaughan, Peterson, & Bingham, 2011). A recent RAND report suggested that healthy sleep is critical to resilience, operationalized as service members' performance and operational readiness, during deployment (Troxel et al., 2015). Despite this growing interest, no consensus definition of resilience has been established nor have any theories describing the relationship between sleep, resilience, and health outcomes been proposed or tested. Further, most research has focused on active duty service members with a paucity of research on the role resilience, particularly when defined as a psychological construct rather than mere outcome, might play in sleep problems among veterans.

Much of the early resilience research was rooted in developmental psychology where researchers largely focused on resilience as a positive outcome in children who had experienced early-life stress or adversity (Garmezy, 1971; Werner, 1995). However, much of this early research only examined major life events or stressors and failed to recognize how daily stressors or hassles, such as strains related to social, occupational, or financial hardships, impact resilience. Much of the stress and coping literature suggests that the cumulative impact of daily hassles is more stressful and more detrimental to an individual's overall psychological and physical health (Charles, Piazza, Mogle, Sliwinski, & Almeida, 2013; DeLongis, Coyne, Dakof, Folkman, & Lazarus, 1982) compared to major life events. Additionally, early resilience research ignored the concept of stress proliferation, or the idea that "stress begets stress," meaning that individuals who experience major life stressors are more susceptible to experiencing the effects of subsequent stressors (Pearlin, Schieman, Fazio, & Meersman, 2005; Pearlin & Skaff, 1996). As suggested earlier, veterans may face a series of stressors during the re-integration period. While not empirically tested to date, it is likely that daily hassles outnumber major life events and that many of these hassles contribute to stress-induced sleep problems, including insomnia. Furthermore, bouts of insomnia may also act as daily hassles in which the cumulative effects of these repeated bouts trigger additional stress and resulting sleep problems.

More contemporary approaches recognize resilience as a dynamic, multilevel, and multicomponent capacity for adapting to stress (Masten, 2001, 2007). This capacity draws on adaptive processes and abilities across behavioral, physiological and psychological systems. Modern conceptualizations of resilience also emphasize the role of health behaviors

including sleep, diet, and physical activity as important contributors to enhancing one's resilience (Southwick, Bonnano, Masten, Panter-Brick, & Yehuda, 2014). By focusing on health behaviors, contemporary research emphasizes the importance of going "upstream" of resilience and working to identify pertinent mechanisms, such as modifiable health behaviors, that can enhance or degrade resilience.

Integrated Theoretical Model

The discussions above suggest that the causes and consequences of insomnia in U.S. military veterans are complex and that sleep may play an important role in longterm mental and physical health. Below, we present an innovative integrated theoretical model that could be used to better understand the growing problem of insomnia among military veterans. This model builds on the 3P Model of Insomnia (Spielman & Glovinsky, 1991). Widely used in clinical assessment and interventions, the 3P Model provides a framework for understanding insomnia through three interrelated, sequential factors – predisposing, precipitating, and perpetuating (see Figure 1). These factors encompass genetic, constitutional, environmental, experiential, and behavioral contributors to sleep problems, respectively. The interaction between and progression across the three factors ("3Ps") transform acute insomnia symptoms into a chronic insomnia disorder.

Although widely regarded as the leading explanatory model of insomnia, the 3P Model could benefit from several additions which are addressed in the remainder of the paper. Our integrated model offers a more thorough understanding of insomnia by exploring the following additions. First, the model provides greater clarification of the mechanisms operating within each of the three factors. Second, unlike the 3P Model that conceptualizes insomnia and sleep problems as a consequence of a stressful event, this model recognizes sleep problems as both a stress response (consequence) and an independent stressor (predictor) that may trigger additional, negative reactions. Third, this model explores both short- and long-term consequences of insomnia, acknowledging its potential effects of insomnia on physiological, psychosocial, and cognitive domains. Finally, this model includes a dimension of time which may encourage additional studying of long-term consequences of sleep, including consideration of stress proliferation and cyclical patterns of increased stress, poor sleep, and negative outcomes that some veterans experience, including those of earlier wars.

The primary aim of the integrated theoretical model presented here (Figure 2) is to encourage a broader conceptualization of insomnia problems in U.S. military veterans. The proposed model integrates and expands upon the three major components of the 3P Model: predisposing (Boxes 1 and 2), precipitating (Box 3), and perpetuating (Box 10) factors. Drawing on constructs from several key behavioral medicine theories (see Figure 1), the model depicts potential mechanisms by which a stressful event (Box 3) contributes to insomnia problems (Box 11), impaired function (Box 12), reduced resilience (Box 13), and poor health outcomes (Box 14). Unlike existing theories that assume only a unidirectional relationship between stressful events and insomnia, our model proposes that insomnia is cyclical in nature. Here, insomnia is a consequence of stress *and* a predictor of additional stress. Insomnia impairs function, which reduces adaptive capacity, thereby increasing one's

risk for subsequent stressful events. Thus, the cycle begins anew, potentially triggering what will become a chronic problem (Pathways U and V). As shown, this model places a particular emphasis on the consequences of chronic, untreated insomnia.

Predisposing factors

Predisposing factors of insomnia refer to modifiable and non-modifiable factors such as a genetic, biological, or psychological vulnerability to stress and/or chronic health problems. The diathesis-stress model suggests individuals possess a diathesis, or predisposing characteristic(s), that increase vulnerability to a negative stress response or outcome (Monroe & Simons, 1991). Such characteristics include genetic risk factors, sociodemographic factors, early trauma, personality traits, and biobehavioral developmental factors including neurological and cognitive functioning. Of note, adverse childhood experiences, including exposure to domestic violence, parental separation or divorce, and emotional or physical abuse, are more common among military servicemembers compared to non-servicemembers (Blosnich, Dichter, Cerulli, Batten, & Bossarte, 2014). Not only are early life events associated with poor physical and mental health outcomes in adulthood (Cabrera, Hoge, Bliese, Castro, & Messer, 2007), they may increase susceptibility to additional stressors, as described in above explanations of stress proliferation. When confronted with subsequent military or non-military stressors (Box 3), both early life events and personal characteristics may increase an individual's risk for negative outcomes.

In addition, the theory of sleep-related stress reactivity posits that individuals with high levels of baseline stress reactivity (i.e., higher basal cortisol levels and more negative/ anxious psychological dispositions) have greater susceptibility to developing insomnia (Box 2) (Drake, Pillai, & Roth, 2014). High sleep-related stress reactivity is positively associated with stress susceptibility and heightened responses across physiological and psychological domains. Stress reactivity is marked by a hyperactive adrenal system (i.e., elevated levels of stress and adrenal hormones) and poor emotional and cognitive regulation, which are manifested in an inability to sleep in a high stress situation (Drake et al., 2004; Harvey, Tang, & Browning, 2005; Perlis, Giles, Mendelson, Bootzin, & Wyatt, 1997). This diathesis, or predisposition to a negative outcome (Box 2), then interacts with a personal or environmental stressor such as military deployment, retirement, or reintegration-related challenges (Box 3) to trigger a stress response, as suggested by the Diathesis-Stress Model (Monroe & Simons, 1991).

Precipitating factors

Precipitating factors represent major life or environmental stressors that trigger insomnia-like sleep problems. As addressed above, it is the interaction between predisposing factors, or diathesis, and an environmental stressor or event (precipitating factor) that triggers a stress response (Monroe & Simons, 1991). Multiple predisposing and precipitating factors can occur sequentially or simultaneously. For some veterans, deployment-related stressors (i.e. combat exposure, service-related injury) may trigger insomnia symptoms, whereas for others, stressors related to military retirement and civilian reintegration (i.e. family obligations, occupational or financial stress, injury and/or rehabilitation challenges) may initiate these symptoms. Additionally, some veterans may experience one major stressor, or

precipitating factor, while others may experience a series, of smaller, daily stressors. It is this accumulation of stressors that serves as the precipitating event for insomnia.

In addition to the interaction noted above, Lazarus and Folkman's Transactional Model of Stress and Coping (Glanz & Schwartz, 2008) builds on the diathesis-stress model to suggest that a stress response depends on a "transaction," or interaction, between the individual and environment. This model emphasizes that an individual's appraisal of a stressor (i.e., precipitating event) vis-à-vis susceptibility and severity (primary appraisal) (Box 4), and perceived ability to cope with a stressor (self-efficacy) (secondary appraisal) (Box 5), directly influence the coping efforts and behaviors he or she chooses to enact (Box 8). These processes are moderated by dispositional coping style (Box 7) and degree of social support (Box 6) and mediated by coping efforts, including the use of problem- or emotion-focused strategies (Box 7). For example, some veterans who perceive military culture as discouraging stress disclosure and/or that military status artificially protects against negative outcomes (Box 4) may be less likely to disclose having experienced a stressful event and therefore less likely to seek help (Box 8). Other veterans may perceive re-integration to be stressful and a trigger for other negative outcomes (i.e. additional family or occupational stress). However, if these individuals do not have strong self-efficacy, social support or coping skills, they may be less likely to seek help for stress-induced insomnia problems (Boxes 8 and 9), and, as a result, experience significant insomnia problems and related consequences. Additional factors may also impact an individual's decision to seek care, including the availability of and access to trained sleep specialists, prior experiences with sleep or other behavioral treatments, and personal treatment preferences.

Perpetuating factors

Acute insomnia problems become chronic through a combination of the perpetuation of unhealthy sleep behaviors and the conditioned arousal resulting from an inability to achieve and/or maintain sleep and the consequential shift in sleep patterns (Pathway O). Perpetuating factors represent unhealthy sleep behaviors used to cope with poor sleep, including following an irregular sleep schedule, spending excessive time in bed even when not sleeping, or increasing alcohol or caffeine intake to either induce sleep or wakefulness, respectively (Box 10) (Morin, 1993; Morin et al., 2006). In line with the constructs of the Transactional Model of Stress and Coping (Glanz & Schwartz, 2008), positive coping efforts reduce insomnia symptoms while negative coping efforts, including those listed above, exacerbate symptoms of poor sleep. Many of these behaviors, including spending time in bed while not sleeping or attaching negative cognitions to an inability to sleep, generate feelings of frustration, fatigue, and anxiety, each of which becomes paired, or conditioned, with the bed and bedroom. Over time, these negative thoughts and behaviors reinforce an inability to initiate and maintain quality, uninterrupted sleep. Such negative associations and reinforcement demonstrate core characteristics of classical and operant conditioning, respectively (Perlis et al., 1997).

Bandura's Social Cognitive Theory (McAlister, Perry, & Parcel, 2008) highlights several constructs central to health behavior and health promotion. When applied to sleep, these constructs aid in further explaining the mechanisms of Spielman's perpetuating factors

(Spielman & Glovinsky, 1991), particularly how cognitions co-occurring with unhealthy sleep behaviors become associated with sleep. First, reciprocal determinism suggests that unhealthy sleep behaviors and a poor sleep environment are bidirectional, constantly influencing and reinforcing one another. Second, prolonged unhealthy behaviors diminish an individual's capacity for self-regulation and self-efficacy for maintaining healthy, restorative sleep behaviors. Finally, chronic problems and frustration associated with not being able to sleep condition an individual's sleep-related outcome expectations to be negative rather than positive. Negative expectations can discourage an individual from reducing unhealthy, maladaptive behaviors in favor of healthier coping strategies.

Proliferation of Sleep Problems

While the 3P Model of Insomnia provides a larger framework for understanding risk, development, and continuation of insomnia, it was not originally designed to address consequences of unresolved or residual sleep problems. The 3P Model suggests insomnia is experienced in a unidirectional, linear fashion and assumes that insomnia is resolved by treating perpetuating factors. Future studies of insomnia, including new iterations of the 3P model, could benefit from a more longitudinal approach. Such an approach should be applied to both epidemiological studies examining trajectories of insomnia and to treatment studies.

Cognitive Behavioral Therapy for Insomnia (CBT-I) is the recommended first-line treatment for insomnia (National Institutes of Health, 2005; Qaseem et al., 2016). CBT-I targets perpetuating factors of insomnia (as shown in Box 10), including unhealthy behaviors and cognitions, and is effective in the short term (12–18 months) (Morin et al., 2006). CBT-I and other behavioral treatments have been shown to effectively reduce insomnia symptoms and severity in veterans (Germain, Shear, Hall, & Buysse, 2007; Karlin, Trockel, Spira, Taylor, & Manber, 2015; Trockel, Karlin, Taylor, & Manber, 2014). However, some veterans continue to have either subthreshold or clinically significant symptoms following treatment (Trockel et al., 2014). The lack of long-term follow-up (i.e. beyond 6 or 12 months after treatment completion) makes it difficult to gauge the longterm trajectories of these individuals and the number who experience future bouts of insomnia. It is unclear whether these residual problems resulted from lack of sufficient follow-up (i.e. participants need additional time to adjust to a new sleep schedule and experience full treatment effects) or whether existing interventions could benefit from one or more revisions (i.e. booster sessions, general coping strategies, or tips for managing high stress reactivity). Additionally, veterans may experience an additional stressor that triggers insomnia after completing a course of CBT-I treatment. Additional research is needed to examine the extent to which prior CBT-I treatment remains effective after experiencing subsequent stressors.

One possible explanation for the chronicity of sleep problems is impaired and/or reduced coping capacity. As addressed in the first portion of this paper, poor sleep contributes to impaired cognitive and functional performance (Box 12). In line with these findings and laboratory studies demonstrating impaired performance following sleep deprivation, it is hypothesized that reduced function resulting from chronic sleep problems also negatively impact an individual's reserve or adaptive capacity to respond to subsequent stressors (Box

12). This prediction is in line with health-related definitions of resilience, defined as a dynamic process of physiological and psychological adaptation to acute and chronic stress (Irwin, 2014; Lavretsky, 2014). Over time, chronic sleep problems, particularly sleep deprivation, lead to an ever-increasing allostatic load on physiological and psychological systems (McEwen, 2006; McEwen & Karatsoseso, 2015), thus contributing to excessive “wear and tear” on the body (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). Increasing allostatic load reduces the likelihood that an individual is able to successfully respond to or cope with subsequent stressors (Juster, McEwen, & Lupien, 2010; McEwen & Karatsoseso, 2015). This reduced stress capacity then contributes to poor physical and psychological health outcomes (Box 14).

There may be benefits to future research examining how impaired coping capacity may interact with high levels of stress reactivity, and what impact this combination of factors may have on future bouts, or relapses, of insomnia. If such an interaction is present, it may be that innovative hybrid interventions, such as those informed by principles of CBT-I and Mindfulness Based Stress Reduction (MBSR) may be effective in targeting both unhealthy sleep behaviors and underlying stress reactivity. MBSR has been shown to reduce physiological and psychological stress reactivity (Sharma & Rush, 2014) and an initial test of one such hybrid program, Mindfulness Based Therapy for Insomnia, which combines principles of CBT-I and MBSR, demonstrated promising results in reducing severity of insomnia symptoms (Ong et al., 2014). Although CBT-I curriculum teaches sleep-related coping strategies, it does not include more general stress and coping strategies. Integrating some of these strategies into behavioral sleep treatments may improve long-term coping and help reduce the likelihood of chronic insomnia.

Future directions

The proposed theoretical model highlights the etiological and clinical complexity of insomnia in U.S. military veterans, placing a particular emphasis on untreated insomnia problems. Severe sleep problems, such as insomnia, might occur at one point in time, typically triggered by a major life or environmental stressor, but their antecedents are found early in life and their consequences can extend for years or decades beyond the triggering stressful event(s). The model presented herein is meant to encourage researchers and clinicians to apply lifespan models to the problems of stress, insomnia, and health outcomes in veterans. While longitudinal data collection is time and resource intensive, such information would allow researchers to better understand the temporal nature and interrelationships between stressful events, sleep problems, and negative physical and psychological outcomes. Although not shown in this model, insomnia may co-occur with other sleep disorders, including sleep disordered breathing, restless leg syndrome, and chronic nightmares. Future iterations of the model should take a holistic approach to sleep and acknowledge these other common sleep disorders.

Sleep problems, particularly insomnia, are often assumed to be an acute consequence of deployment or reintegration. However, this model highlights the potential cyclical nature of insomnia, noting that chronic problems can deleteriously impact veterans’ long-term health and function. This model also highlights the importance of studying major life events and

daily stressors as both predictors and consequences of insomnia problems. Finally, as alluded to above, sleep and resilience are likely important yet under-studied mechanisms in veterans' long-term health. Additional research focusing on the multidimensional nature of resilience, including how physiological and psychological adaptive capacities contribute to an individual's stress response, is warranted. Future research examining these relationships and mechanisms could prove fruitful in both clinical and research settings, particularly as an increasing number of OEF/OIF veterans retire from military service and begin to utilize both VA and community healthcare services. As our theoretical model suggests, addressing sleep problems early could potentially enhance a veteran's adaptive capacity, thereby reducing the risk for negative physical and psychological outcomes across the lifespan. Finally, the constructs and mechanism outlined in this particular model may have application to non-veterans, including individuals who have experienced a significant life stressor or traumatic event. Future iterations of the model should highlight the mechanisms of insomnia and comorbid mental and physical health conditions.

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Abbreviations

VHA	Veterans Health Administration
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
PTSD	Post-traumatic Stress Disorder
CBT-I	Cognitive Behavioral Therapy for Insomnia

References

- Ahn S, Jiang L, Smith ML, Ory MG. Improvement in sleep problems among the chronic disease self-management program participants. *Family & Community Health*. 2014; 27(4):327–355.
- American Psychiatric Association. *Desk Reference to the Diagnostic Criteria from DSM-5*. Arlington, VA: American Psychiatric Association; 2013.
- Amin M, Parisi JA, Gold MS, Gold AR. War-related illness symptoms among Operation Iraqi Freedom/Operation Enduring Freedom returnees. *Military medicine*. 2010; 175(3):155–157. [PubMed: 20358703]
- Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholdzer U, Riemann D. Insomnia as a predictor of depression: A meta-analytic evaluation of longitudinal epidemiological studies. *Journal of Affective Disorders*. 2011; 135:10–19. [PubMed: 21300408]

- Benight CC, Bandura A. Social cognitive theory of posttraumatic recovery: the role of perceived self-efficacy. *Behaviour research and therapy*. 2004; 42:1129–1148. [PubMed: 15350854]
- Blosnich JR, Dichter ME, Cerulli C, Batten SV, Bossarte RM. Disparities in Adverse Childhood Experiences Among Individuals with a History of Military Service. *JAMA Psychiatry*. 2014; 71(9): 1041–1048. [PubMed: 25054690]
- Bramoweth AD, Germain AA. Deployment-related insomnia in military personnel and Veterans. *Current Psychiatry Reports*. 2013; 15:401–409. [PubMed: 24005883]
- Breslau N, Roth T, Rosenthal L, Andreski PM. Sleep disturbance and psychiatric disorders: A longitudinal study of young adults. *Biological Psychiatry*. 1996; 39(6):411–418. [PubMed: 8679786]
- Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research*. 1989; 23:193–213.
- Cabrera OA, Hoge CW, Bliese PD, Castro CA, Messer SC. Childhood adversity and combat as predictors of depression and post-traumatic stress in deployed troops. *American Journal of Preventive Medicine*. 2007; 33(2):77–82. [PubMed: 17673093]
- Campbell, J., Shattuck, N., Germain, A., Mysliwiec, V. Introduction; Paper presented at the 29th Annual Meeting of the Association of Professional Sleep Societies; Seattle, WA. 2015.
- Castro CA, Kintzle S, Hassan AM. The combat veteran paradox: Paradoxes and dilemmas with reintegrating combat veterans and the agencies that support them. *Traumatology*. 2015; 22(4): 299–310.
- Charles ST, Piazza JR, Mogle J, Sliwinski MJ, Almeida DM. The wear and tear of daily stressors on mental health. *Psychological Science*. 2013; 34(4):733–741.
- DeLongis A, Coyne JC, Dakof G, Folkman S, Lazarus RS. Relationship of daily hassles, uplifts, and major life events to health status. *Health Psychology*. 1982; 1(2):119–136.
- Dement, WC., Vaughan, C. The promise of sleep: A pioneer in sleep medicine explores the vital connection between health, happiness, and a good night’s sleep. New York, NY: Dell Publishing Co; 1999.
- Dew MA, Hoch CC, Buysse DJ, Monk TH, Begley A, Houck PR, Reynolds CF. Healthy older adults’ sleep predicts all-cause mortality at 4 to 19 years of follow-up. *Psychosomatic medicine*. 2003; 65:63–73. [PubMed: 12554816]
- Drake CL, Friedman NP, Wright KP, Roth T. Sleep reactivity and insomnia: Genetic and environmental influences. *Sleep*. 2011; 34(9):1179–1188. [PubMed: 21886355]
- Drake CL, Pillai V, Roth T. Stress and sleep reactivity: A prospective investigation of the stress-diathesis model of insomnia. *Sleep*. 2014; 37(8):1295–1304. [PubMed: 25083009]
- Drake CL, Richardson G, Roerhs T, Scofield N, Roth T. Vulnerability to stress-related sleep disturbance and hyperarousal. *Sleep*. 2004; 27(2):285–291. [PubMed: 15124724]
- Fernandez-Mendoza J, Vgontzas AN. Insomnia and its impact on physical and mental health. *Current Psychiatry Reports*. 2013; 15:418–426. [PubMed: 24189774]
- Ford D, Kamerow D. Epidemiologic study of sleep disturbances and psychiatric disorders: An opportunity for prevention? *Journal of the American Medical Association*. 1989; 262(11):1479–1484. [PubMed: 2769898]
- Ford E, Cunningham T, Giles W, Croft J. Trends in insomnia and excessive daytime sleepiness among US adults from 2002 to 2012. *Sleep Medicine*. 2015; 16(3):372–378. [PubMed: 25747141]
- Garzezy M. Vulnerability research and the issue of primary prevention. *American Journal of Orthopsychiatry*. 1971; 41(1):101–116. [PubMed: 5539483]
- Gehrman P, Seelig AD, Jacobson IG, Boyko EJ, Hooper TI, Gackstetter GD. Millennium Cohort Study Team. Predeployment sleep duration and insomnia symptoms as risk factors for new-onset mental health disorders following military deployment. *Sleep*. 2013; 36(7):1009–1018. [PubMed: 23814337]
- Germain A, Shear MK, Hall M, Buysse DJ. Effects of a brief behavioral treatment for PTSD-related sleep disturbances: a pilot study. *Behaviour research and therapy*. 2007; 45:627–632. [PubMed: 16777060]

- Glanz, K., Schwartz, MD. Stress, coping, and health behavior. In: Glanz, K., Rimer, BK., Viswanath, K., editors. *Health Behavior and Health Education*. San Francisco, CA: Jossey-Bass; 2008. p. 211-236.
- Hamilton NA, Delwyn C, Karlson C. Sleep and the affective response to stress and pain. *Health Psychology*. 2007; 26(3):288–295. [PubMed: 17500615]
- Harvey AG, Tang NKY, Browning L. Cognitive approaches to insomnia. *Clinical Psychology Review*. 2005; 25:593–611. [PubMed: 15979771]
- Haynes PL, Parthasarathy S, Bootzin RR, Krakow B. Motivational enhancement therapy for insomnia in OEF/OIF Veterans: A treatment development study. *Sleep*. 2013; 36(Supplement):A232.
- Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in US soldiers returning from Iraq. *New England Journal of Medicine*. 2008; 358:453–463. [PubMed: 18234750]
- Hoge E, Austin E, Pollack M. Resilience: Research evidence and conceptual considerations for Posttraumatic Stress Disorder. *Depression and Anxiety*. 2007; 24:139–152. [PubMed: 16892420]
- Hughes J, Martin JL. Sleep characteristics in Veterans Affairs Adult Day Health Care participants. *Behavioral Sleep Medicine*. 2015; 13(3):197–207. [PubMed: 24654988]
- Institute of Medicine. *Returning home from Iraq and Afghanistan: Assessment of readjustment needs of Veterans, service members, and families*. Washington, DC: National Academies Press; 2013.
- Irwin MR. Sleep and inflammation in resilient aging. *Interface Focus*. 2014; 4
- Juster R, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience and Biobehavioral Reviews*. 2010; 35:2–16. [PubMed: 19822172]
- Karlin BE, Trockel M, Spira AP, Taylor CB, Manber R. National evaluation of the effectiveness of cognitive behavioral therapy for insomnia among older versus younger veterans. *International Journal of Geriatric Psychiatry*. 2015; 30:308–315.
- Katz DA, McHorney CA. The relationship between insomnia and health-related quality of life in patients with chronic illness. *Journal of Family Practice*. 2002; 51(3):229–235. [PubMed: 11978233]
- Killgore WDS, Balkin TJ, Westenssten NJ. Impaired decision making following 49 hours of sleep deprivation. *Journal of Sleep Research*. 2006; 15(1):7–13. [PubMed: 16489997]
- Killgore WDS, Kahn-Greene, Lipizzi EL, Newman RA, Kamimori GH, Balkin TJ. Sleep deprivation reduces perceived emotional intelligence and constructive thinking skills. *Sleep medicine*. 2008; 9(5):517–526. [PubMed: 17765011]
- Koffel E, Thuras P, Chakravorty S, Germain A, Khawakaja I. Poor sleep quality as a predictor of readmission to a psychiatry partial hospitalization program. *Sleep*. 2015; 38(Supplement):A326.
- Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality Associated With Sleep Duration and Insomnia. *Archives of General Psychiatry*. 2002; 59:131–136. [PubMed: 11825133]
- Lavretsky, H. *Resilience and Aging: Research and Practice*. Baltimore, MD: Johns Hopkins University Press; 2014.
- Lohr JB, Palmer BW, Eids CA, Aaliaboyina S, Mausbach BT, Wolkowitz OM, Jeste DV. Is Post-Traumatic Stress Disorder associated with premature senescence? A review of the literature. *American Journal of Geriatric Psychiatry*. 2015; 23(7):709–725. [PubMed: 25959921]
- Macera CA, Aralis HJ, Rauch MJ, MacGregor AJ. Do sleep problems mediate the relationship between traumatic brain injury and development of mental health symptoms after deployment? *Sleep*. 2013; 36:83–90. [PubMed: 23288974]
- Marmar CR. Mental health impact of Afghanistan and Iraq deployment: Meeting the challenge of a new generation of Veterans. *Depression and Anxiety*. 2009; 26(6):493–497. [PubMed: 19484716]
- Marmar CR, Schlenger WE, Henn-Haase C, Qian M, Puchia E, Li M, Kulka RA. Course of posttraumatic stress disorder 40 years after the Vietnam war: Findings from the National Vietnam Veterans Longitudinal Study. *JAMA Psychiatry*. 2015; 72(9):875–881. [PubMed: 26201054]
- Masten AS. Ordinary magic: Resilience processes in development. *American Psychologist*. 2001; 56(3):227–238. [PubMed: 11315249]
- Masten AS. Resilience in development systems: Progress and promise as the fourth wave rises. *Development and Psychopathology*. 2007; 19:921–930. [PubMed: 17705908]

- McAlister, AL., Perry, CL., Parcel, GS. How individuals, environments, and health behaviors interact: Social cognitive theory. In: Glanz, K.B Rimer, K., Viswanath, K., editors. *Health Behavior and Health Education*. San Francisco, CA: Jossey-Bass; 2008. p. 167-188.
- McEwen BS. Sleep deprivation as a neurobiologic and physiologic stressor: Allostasis and allostatic load. *Metabolism Clinical and Experimental*. 2006; 55(Suppl 2)
- McEwen BS, Karatsoreso IN. Sleep deprivation and circadian disruption: Stress, allostasis, and allostatic load. *Sleep Medicine Clinics*. 2015; 10:1–10. [PubMed: 26055668]
- Monroe SM, Simons AD. Diathesis-stress theories in the context of life research: Implications for the depressive disorders. *Psychological bulletin*. 1991; 110:406–425. [PubMed: 1758917]
- Morin, C. *Insomnia: Psychological Assessment and Management*. New York: The Guilford Press; 1993.
- Morin C, Bootzin R, Buysse DJ, Edinger JD, Espie CA, Lichstein KL. Psychological and behavioral treatment of insomnia: Update of the recent evidence. *Sleep*. 2006; 29(11):1398–1414. [PubMed: 17162986]
- Morin C, Ivers H. Role of stress, arousal, and coping skills in primary insomnia. *Psychosomatic medicine*. 2003; 65(259–267)
- Mysliwiec V, McGraw PR, Smith P, Trapp B, Roth BJ. Sleep disorders and associated medical comorbidities in active duty military personnel. *Sleep*. 2013; 36(2):167–174. [PubMed: 23372263]
- National Institutes of Health. NIH State-of-the-Science Conference Statement on the Manifestations and Management of Chronic Insomnia in Adults. 2005 Retrieved from Bethesda, MD:
- Ong JC, Manber R, Segal Z, Zia Y, Shapiro S, Wyatt JK. A randomized controlled trial of mindfulness meditation for chronic insomnia. *Sleep*. 2014; 37(9):1153–1563.
- Pearlin LI, Schieman S, Fazio EM, Meersman SC. Stress, Health, and the Life Course: Some Conceptual Perspectives. *Journal of health and social behavior*. 2005; 46:205–219. [PubMed: 16028458]
- Pearlin LI, Skaff MM. Stress and the Life Course: A Paradigmatic Alliance. *The Gerontologist*. 1996; 36(2):239–247. [PubMed: 8920095]
- Perlis ML, Giles DE, Mendelson WB, Bootzin RR, Wyatt JK. Psychophysiological insomnia: The behavioural model and a neurocognitive perspective. *Journal of Sleep Research*. 1997; 6:179–188. [PubMed: 9358396]
- Perlis ML, Smith LJ, Lyness JM, Matteson SR, Pigeon WR, Jungquist C. Insomnia as a risk factor for onset of depression in the elderly. *Behavioral Sleep Medicine*. 2006; 4:104–113. [PubMed: 16579719]
- Peterson AL, Goodie JL, Satterfield WA, Brim WL. Sleep disturbance during military deployment. *Military medicine*. 2008; 173(230):235.
- Pigeon, WR., Britton, P., Ilgen, MA., Chapman, B., Conner, KR. Sleep disturbance preceding suicide among Veterans. In: Bossarte, RM., editor. *Veteran suicide: A public health imperative*. Washington, D.C: American Public Health Association; 2013. p. 278-288.
- Pigeon WR, Piquart M, Connor K. Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *Journal of Clinical Psychiatry*. 2012; 73(9):e1160–e1167. [PubMed: 23059158]
- Pigeon WR, Unutzer J, Perlis ML. Is insomnia a perpetuating factor for late-life depression in the IMPACT cohort? *Sleep*. 2008; 31(4):481–488. [PubMed: 18457235]
- Pilcher JJ, Huffcutt AJ. Effects of sleep deprivation on performance: A meta-analysis. *Journal of Sleep Research & Sleep Medicine*. 1996; 19(4):318–326.
- Qaseem A, Kansagara D, Forcica MA, Cooke M, Denberg TD. Clinical Guidelines Committee of the American College of Physicians. Management of chronic insomnia disorder in adults: A clinical practice guideline from the American College of Physicians. *Annals of Internal Medicine*. 2016; 165:125–133. [PubMed: 27136449]
- Roth T. Insomnia: Definition, prevalence, etiology, and consequences. *Journal of Clinical Sleep medicine*. 2007; 3(5):S7–S10. [PubMed: 17824495]
- Ryden AM, Matsuwaka S, Mitchell MN, Fung CH, Dzierzewski JM, Song Y, Alessi CA. Prevalence of insomnia disorder decreases with age among older Veterans. *Sleep*. 2015; 38(Supplement):A396.

- Schnurr PP, Spiro A III, Paris AH. Physician-Diagnosed Medical Disorders in Relation to PTSD Symptoms in Older Male Military Veterans. *Health Psychology*. 2000; 10(1):91–97.
- Seelig AD, Jacobson IG, Donoho CJ, Trone DW, Crum-Cianflone NF, Balkin TJ. Sleep and health resilience metrics in a large military cohort. *Sleep*. 2016; 39(5):1111–1120. [PubMed: 26951391]
- Seelig AD, Jacobson IG, Smith B, Hooper TI, Boyko EJ, Gackstetter GD, Smith TC. Sleep patterns before, during, and after deployment to Iraq and Afghanistan. *Sleep*. 2011; 33(12):1615–1622.
- Seeman TE, Singer BH, Rowe JW, Horwitz RI, McEwen BS. Price of adaptation--allostatic load and its consequences: MacArthur studies of successful aging. *Archives of Internal Medicine*. 1997; 157:2259–2268. [PubMed: 9343003]
- Sharma M, Rush SE. Mindfulness-based stress reduction as stress management intervention for healthy individuals: A systematic review. *Journal of Evidence-Based Complementary & Alternative Medicine*. 2014; 19(4):271–286. [PubMed: 25053754]
- Shippee ND, Shah ND, May CR, Mair FS, Montori VM. Cumulative complexity: A functional, patient-centered model of patient complexity can improve research and practice. *Journal of Clinical Epidemiology*. 2012; 65(1041–1051)
- Southwick SM, Bonnano GA, Masten AS, Panter-Brick C, Yehuda R. Resilience definitions, theory, and challenges: interdisciplinary perspectives. *European Journal of Psychotraumatology*. 2014; 5:1–15.
- Spielman, A., Glovinsky, PB. The varied nature of insomnia. In: Hauri, PJ., editor. *Case studies in insomnia*. New York, NY: Plenum Press; 1991. (Reprinted from: NOT IN FILE)
- Stanley EA, Schaldach JM, Kiyonga A, Jha AP. Mindfulness-based mind fitness training: A case study of a high-stress predeployment military cohort. *Cognitive and Behavioral Practice*. 2011; 18(566–576)
- Taylor DJ, Mallory LJ, Lichstein KL, Durrence HH, Riedel BW, Bush AJ. Comorbidity of Chronic Insomnia with Medical Problems. *Sleep*. 2007; 30(2):213–218. [PubMed: 17326547]
- Trockel M, Karlin BE, Taylor C, Manber R. Cognitive Behavioral Therapy for Insomnia with Veterans: Evaluation of effectiveness and correlates of treatment outcomes. *Behaviour research and therapy*. 2014; 53:41–46. [PubMed: 24412462]
- Troxel WM, Shih RA, Pedersen ER, Geyer L, Fisher MP, Griffin BA, Steinberg PS. *Sleep in the Military: Promoting Healthy Sleep Among U.S. Servicemembers*. 2015 Retrieved from Santa Monica, CA:
- Ulmer CS, Van Voorhees E, Germain AE, Voils CI, Beckham JC. VA Mid -Atlantic Mental Illness Research Education and Clinical Center Registry Workgroup. A comparison of sleep difficulties among Iraq/Afghanistan Theater Veterans with and without mental health diagnoses. *Journal of Clinical Sleep medicine*. 2015; 11(9):995–1005. [PubMed: 26094928]
- Werner EE. Resilience in development. *Current Directions in Psychological Science*. 1995; 43(3):81–85.
- Wolf EJ, Logue MW, Hayes JP, Sadeh N, Schichman SA, Stone A, Miller MW. Accelerated DNA methylation age: Associations with PTSD and neural integrity. *Psychoneuroendocrinology*. 2016; 63:155–162. [PubMed: 26447678]
- Wright KM, Britt TW, Bliese PD, Adler AB, Picchioni D, Moore D. Insomnia as predictor versus outcome of PTSD and depression among Iraq combat veterans. *Journal of clinical psychology*. 2011; 67(12):1240–1258. [PubMed: 22065464]
- Yoon J, Schott JY, Phibbs CS, Wagner TH. Recent trends in Veterans Affairs chronic condition spending. *Population Health Management*. 2011; 14(6):293–298. [PubMed: 22044350]
- Young-McCaughan S, Peterson AL, Bingham MO. The role of sleep in the health and resiliency of military personnel. 2011 Retrieved from Brussels:
- Yu W, Ravelo A, Wagner TH, Phibbs CS, Bhandari A, Chen S, Barnett PG. Prevalence and costs of chronic conditions in the VA health care system. *Medical Care Research and Review*. 2003; 60(3 Suppl):146S–167S. [PubMed: 15095551]
- Zullig LL, Whitson HE, Hastings SN, Beadles C, Kravchenko J, Akushevich I, Maciejewski ML. A systematic review of conceptual frameworks of medical complexity and new model development. *Journal of General Internal Medicine*. 2016; 31(3):329–337. [PubMed: 26423992]

Highlights

- Chronic insomnia problems are highly prevalent among US military Veterans
- Existing theoretical models view insomnia as a unidirectional phenomenon
- An integrated model is proposed that explains insomnia as a chronic, cyclical problem
- Insomnia should be viewed as a both a consequence and predictor of stress

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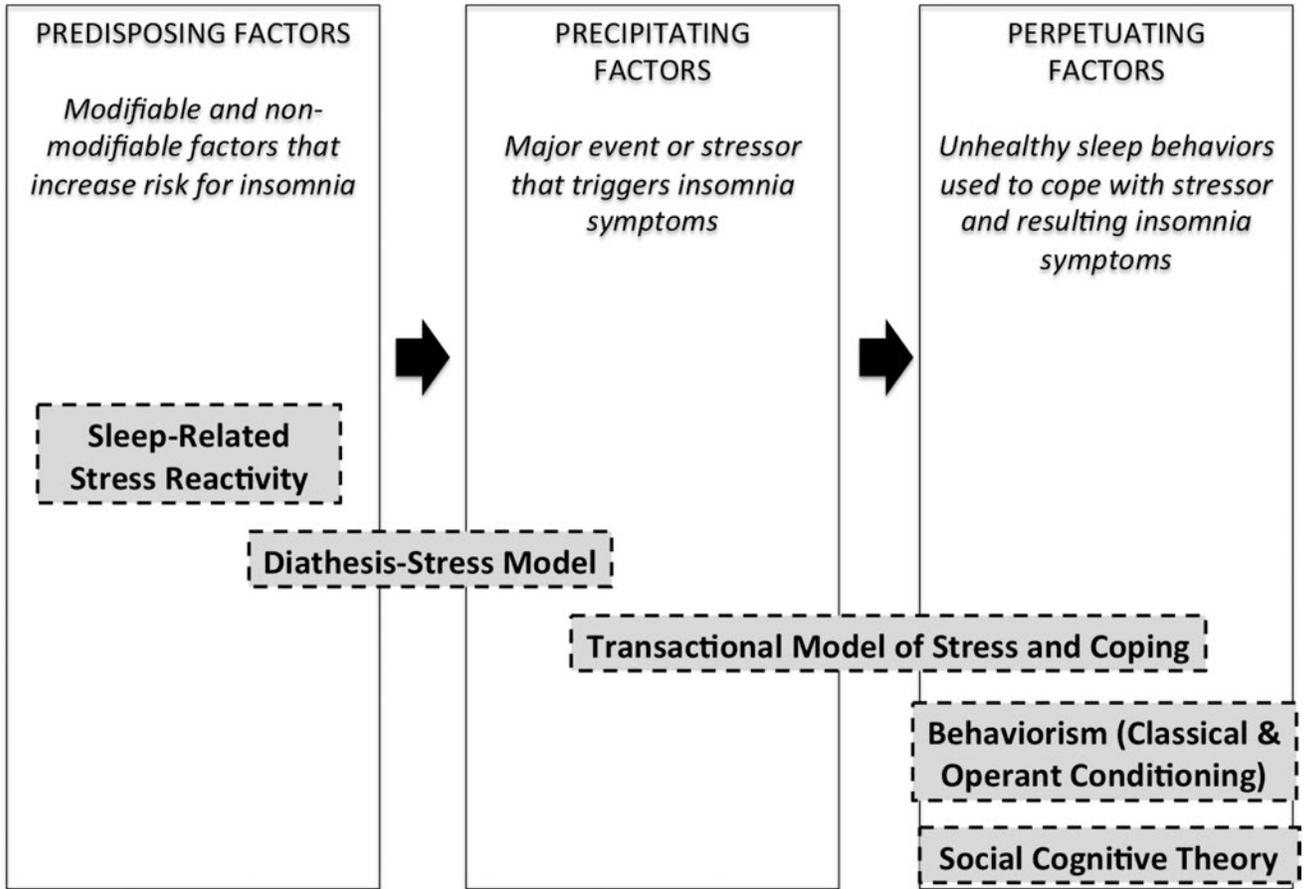


Figure 1. 3P Model of Insomnia: Original Framework and Integrated Theories

Description: This model displays the three factors of the 3P Model of Insomnia – predisposing, precipitating, and perpetuating – as well as the series of behavioral health theories that are used to further describe these three factors.

Footnote: **NOTE: Original factors of 3P model enclosed in boxes outlined in solid lines. Authors’ original integration are indicated by dashed lines. The additions to this model are meant to highlight mechanisms responsible for each of the three factors and to demonstrate the overlap between and transition from one factor to the next.*

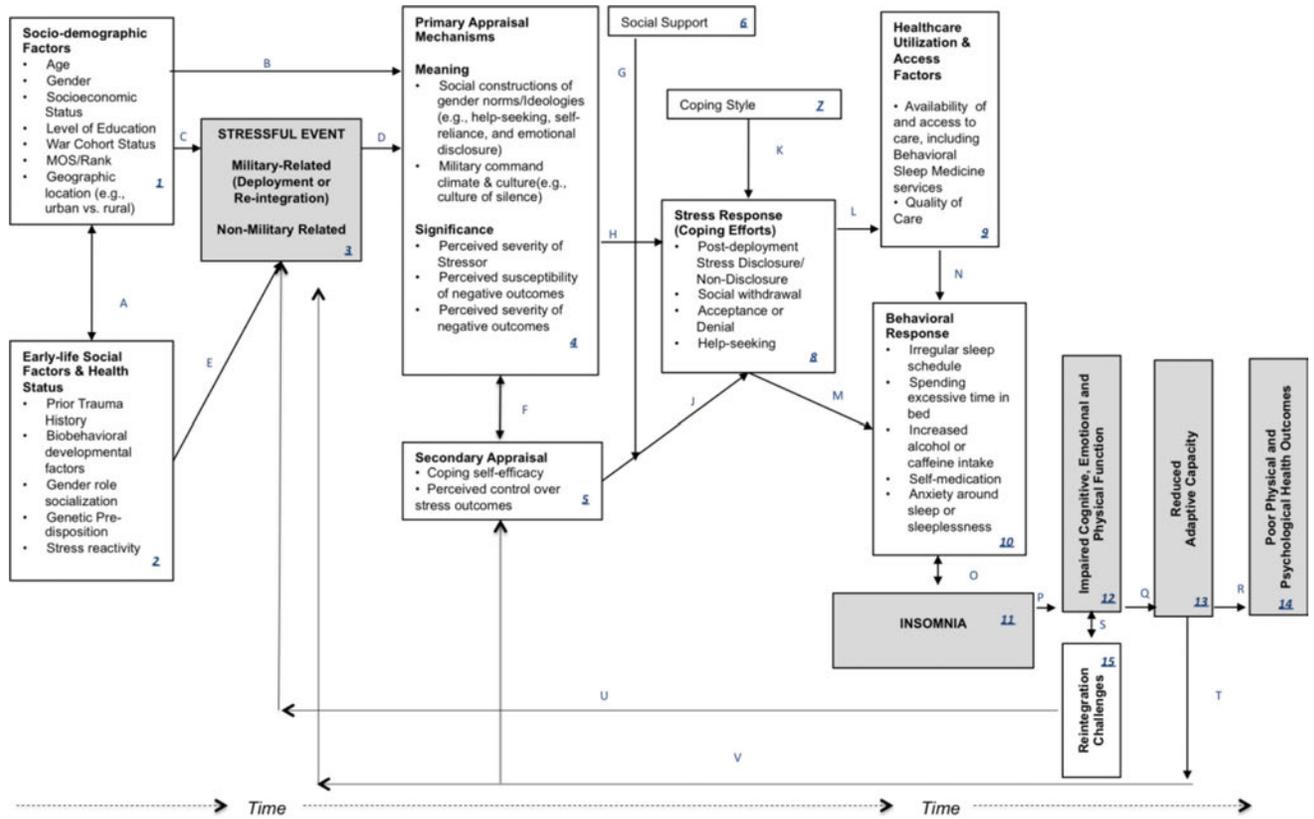


Figure 2. Integrated Theoretical Model of Insomnia Problems in US Military Veterans
 Description: This figure displays an integrated conceptual model of insomnia. This model utilizes constructs from various behavioral health theories to illustrate the cyclical nature of insomnia in United States military Veterans.

Research Article

Residual Effects of Sleep Medications Are Commonly Reported and Associated with Impaired Patient-Reported Outcomes among Insomnia Patients in the United States

Timothy Fitzgerald¹ and Jeffrey Vietri²

¹Merck & Co., Whitehouse Station, NJ 08889, USA

²Kantar Health, 20121 Milan, Italy

Correspondence should be addressed to Jeffrey Vietri; jeffrey.vietri@kantarhealth.com

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Study Objective. To measure the association of symptoms attributed to residual effects of sleep medication (e.g., drowsiness, difficulty concentrating, and impaired memory) on self-reported functioning and satisfaction with these medications. *Methods.* Individuals using prescription medications for insomnia were invited to complete an Internet-based survey. Respondents were compared according to the presence of self-reported residual effects; relationships between severity of these effects and outcomes were modeled using regression. Measures included the Brief Insomnia Questionnaire, Work Productivity and Activity Impairment Questionnaire, and SATMED-Q. Subgroup analyses were conducted with patients aged ≥ 65 years. Approximately 80% reported experiencing ≥ 1 residual effect. The severity of residual effects was associated with increased residual effect-related work impairment, including absenteeism (RR = 1.46, $p < 0.001$), presenteeism (RR = 1.12, $p < 0.001$), overall work impairment (RR = 1.13, $p < 0.001$), and nonwork activity impairment (RR = 1.11, $p < 0.001$). More severe residual symptoms were also associated with increased difficulty in home management (Beta = .31, $p < 0.001$), ability to work (Beta = .31, $p < 0.001$), social relationships, (Beta = .32, $p < 0.001$), close personal relationships (Beta = .30, $p < 0.001$), and lower medication satisfaction (Beta = $-.37$, $p < 0.001$). *Conclusions.* Individuals using medications for insomnia commonly experience symptoms considered as residual effects, and these symptoms are associated with greater interference of sleep-related problems at work, at home, and with social relationships.

1. Introduction

Insomnia is a debilitating condition that accompanies several sleep, medical, and psychiatric disorders. It is diagnosed via subjective reports of persistent difficulty falling asleep, staying asleep, and/or experiencing sleep of poor quality. Insomnia confers significant daytime symptoms such as fatigue, low energy, impaired cognitive functioning, mood disturbance, and perceptions of decreased global functioning. In fact, daytime symptoms are those which most frequently lead patients to seek treatment [1]. Acute insomnia regularly occurs with life events or sleep schedule changes. For some, however, insomnia becomes unrelenting and chronic. Overall, insomnia has become a prevalent and costly public health

concern, associated with long-term effects on functioning and quality of life.

Approximately 25% of U.S. adults report dissatisfaction with their sleep, 10–15% report insomnia symptoms, and 6–10% have an insomnia disorder [2]. Population-based longitudinal data show nearly 70% of patients with baseline insomnia also report insomnia one year later, and 50% of those with baseline insomnia continue to report insomnia up to three years later [3, 4]. In fact, insomnia has become one of the most prevalent complaints in the primary care setting [5]. Moreover, high rates of comorbidity between insomnia and medical/psychiatric disorders have been described. Odds ratios reported by the 2002 U.S. National Health Interview Survey and the U.S. National Comorbidity Survey showed those with

insomnia to be twice as likely to present with congestive heart failure and up to five times more likely to present with a psychiatric disorder [6, 7]. Further, insomnia is strongly associated with hypertension and pain conditions, as well as greater risk of mortality, specifically in older adults [8–10].

Treatment can consist of behavioral/psychological interventions and/or pharmacotherapy. In general, it is considered that primary insomnia and secondary insomnia respond to both pharmacotherapy and behavioral/psychological intervention [11, 12]. Common agents to treat insomnia include over-the-counter agents (OTCs, antihistamines, melatonin, and herbal preparations), prescription hypnotic drugs (benzodiazepines, BzRAs, chronobiotic agents, and low-dose doxepin hydrochloride), and other prescription agents not specifically indicated for insomnia (antidepressants, antipsychotics, and anticonvulsants) [13]. However, sleep-promoting agents can produce adverse effects, particularly in the elderly [13]. Residual sleep medication effects have the potential to interfere with quality of life and include drowsiness, difficulty concentrating, headaches, nausea, dry mouth, oversleeping, and nightmares. Memory can also be affected, including impaired short-term memory and periods of amnesia reported in the literature [14–16].

Of the hypnotics, benzodiazepines and nonbenzodiazepine hypnotics with longer half-lives tend to produce residual impairment or “hang over,” particularly with middle-of-the-night dosing and regular use [17, 18]. Residual effects of hypnotics include sedation, cognitive impairment, motor incoordination, ataxia, dizziness, and gastrointestinal upset. In the elderly, the use of sedating drugs is dangerously associated with increased fall risk [19]. Meanwhile, the use of some antidepressants to treat insomnia has been associated with increased suicidal ideation, increased mania/hypomania in patients with bipolar disorder, and exacerbation of restless legs syndrome [20]. Further, the use of anticonvulsants (e.g., pregabalin) can produce daytime sedation, dizziness, and cognitive impairment [13]. Finally, the use of antipsychotics has been correlated with exacerbation of restless legs syndrome and increased mortality, particularly in elderly individuals [11]. From the standpoint of concern for public safety, insomnia treatments have been shown to impair next-day driving and increase the risk of motor vehicle accidents, particularly in women [21].

As above, older patients are particularly vulnerable to residual sleep medication effects. Meta-analysis of patients aged 60 years and older, who were free of other psychiatric disorders ($N = 2,417$), showed significantly higher odds of adverse cognitive events, adverse psychomotor effects, and daytime fatigue when patients used any hypnotic sedative, compared with placebo [22]. A large ($N = 15,528$) study of nursing home patients (mean age = 81), with hip fracture documented in Medicare Part A and Part D fee-for-service claims, showed elevated risk of hip fracture among users of a nonbenzodiazepine hypnotic sleep drug. Effects were particularly strong in new users [23].

Ultimately, residual sleep medication effects are associated with impaired functioning and lowered quality of life in insomnia patients and confer safety risks for both the patients and the public. Moreover, the literature reports older

patients to be at heightened risk for adverse side effects [13]. Little research, however, has characterized the impact of adverse side effects across multiple domains of functioning in the same group of patients—particularly in the elderly. The current study was conducted to collect information on the relationship between self-reported residual effects of prescription sleep medications and patient-reported outcomes. A secondary objective of the study was to describe the relationship between these symptoms and outcomes in users of these medications aged 65 years and older, since, as described above, these patients may be particularly vulnerable to residual effects [13].

2. Materials and Methods

The present study was a cross-sectional survey of current and former users of prescription medications for sleep reporting a diagnosis of insomnia ($N = 2,250$). For the purpose of estimating the burden of residual effects, only those currently using a sleep medication ($n = 1,605$) were included. Those reporting residual sleep medication effects were compared to those reporting no residual effects, and the relationship between severity of residual effects and outcomes was modeled using regression. Subgroup analyses were conducted with patients aged 65 years or older due to reported vulnerability to adverse sleep medication effects [13].

Respondents were recruited primarily from previous respondents to the U.S. National Health and Wellness Survey (NHWS). The NHWS is a cross-sectional survey administered via the Internet to a sample of adults (18 years and older) who were identified through a web-based consumer survey panel. Members of the panel are recruited through opt-in emails, coregistration with other panels, e-newsletter campaigns, and online banner placements. All panelists explicitly agreed to become panel members, registered through unique email addresses, and completed in-depth demographic registration profiles. Invitations to participate in the NHWS were sent using a random stratified sampling framework to ensure the final sample of NHWS participants is representative of the adult population in the U.S. according to the Current Population Survey (CPS) of the U.S. Census (United States Bureau of the Census, 2012) in terms of age, gender, and white/non-white racial identification. Because of the size of the target sample and inclusion criteria of this study, additional respondents were also identified through the Light Speed Research Ailment Panel, which is composed of general panel members who have self-identified as having certain medical conditions.

Only those who were aged 18 years or older, self-reported a diagnosis of insomnia, and did not self-report diagnosis for sleep-disordered breathing, narcolepsy, shift work disorder, parasomnia, or other sleep condition were included in the survey. For inclusion in the current analysis, respondents also had to report current use of a prescription medication for sleep.

2.1. Procedure. Respondents were interviewed through a self-administered, Internet-based questionnaire between December 5th and 18th, 2012. The protocol and questionnaire

were reviewed and approved by Essex Institutional Review Board (Lebanon, New Jersey, USA) prior to recruitment of participants.

The presence and severity of residual effects were assessed through a series of items assessing to what extent the respondent experienced each of the nine side effects when they take their insomnia medication. These were feelings of drowsiness, difficulty concentrating, difficulty remembering, headaches, nausea, dry mouth, oversleeping, amnesia, and nightmares, using a Likert scale from 1 (None) to 5 (“Very Severe”). Drowsiness, difficulty concentrating, difficulty remembering, headaches, nausea, dry mouth, and oversleeping were also combined by summing the ratings of severity to provide an overall index of residual symptoms.

Respondents who indicated at least one residual symptom completed the Work Productivity and Activity Impairment, Specific Health Problem (WPAI-SHP) questionnaire [24]. The specific health problem was residual symptoms, and the term used in the instrument for residual symptoms was “next-day effects.” Respondents were informed that this term was meant to indicate any side effects they feel the day after taking the medication. Four subscales (absenteeism, presenteeism, overall work impairment, and activity impairment) were generated in the form of percentages, with higher values indicating greater impairment. Absenteeism represents the percentage of work time missed due to next-day effects of sleep medication in the past seven days, and presenteeism represents the percentage of impairment in the past seven days while at work. Overall work impairment represents the overall amount of impact to work productivity due to either absenteeism or presenteeism (since they are mutually exclusive) in the past seven days. Activity impairment represents the percentage of impairment experienced during daily activities in the past seven days. Only employed respondents provided data on absenteeism, presenteeism, and overall work impairment but all respondents who reported at least one residual symptom rated their activity impairment.

Information on sleep difficulties was assessed using the Brief Insomnia Questionnaire (BIQ [25]). Information collected in the BIQ included in this analysis was the number of nights out of the past 7 with sleep problems due to trouble falling asleep, trouble staying asleep, trouble waking too early, waking feeling tired or unrested, and nights with at least one of these problems. The degree to which the individual’s sleep problems interfered with home management, ability to work, social relationships, and close personal relationships was also assessed in the BIQ using a modified version of the Sheehan Disability Scales. These are scored from 0 to 10, with higher numbers indicating greater interference. A “don’t know” response is also provided, and those who selected this option were excluded from analysis of the relevant item.

Insomnia Treatment History. A variety of items were used to characterize the respondents’ treatment history for insomnia. These include the year diagnosed with insomnia, type of diagnosing doctor, type of prescribing doctor, type of doctor currently managing insomnia, whether the respondent is

currently seeing a healthcare provider for insomnia, and previous prescription medications taken for insomnia.

Satisfaction with current medication was measured by the SATMED-Q [26]. This scale includes a total of 17 items that measure treatment satisfaction across multiple domains, including the presence and interference caused by side effects, the efficacy of the medication, convenience and ease of use, impact of medicine on everyday life, the follow-up from the doctor, and the patient’s overall opinion of the medicine.

Health characteristics and risk behaviors incorporated in the analysis included body mass index (BMI; underweight, normal weight, overweight, and obese), alcohol consumption (consume alcohol versus abstain from alcohol), cigarette smoking (current smoker versus nonsmoker), and whether the person reports exercising vigorously in the past 30 days. The severity of respondents’ comorbid medication conditions was assessed using the Charlson comorbidity index (CCI [27]). The CCI is calculated by weighting the presence of the following conditions and summing the result: HIV/AIDS, metastatic tumor, lymphoma, leukemia, any tumor, moderate/severe renal disease, hemiplegia, diabetes, mild liver disease, ulcer disease, connective tissue disease, chronic pulmonary disease, dementia, cerebrovascular disease, peripheral vascular disease, myocardial infarction, and congestive heart failure. The greater the total index score, the greater the comorbidity burden on the patient. Because insomnia commonly presents with psychiatric disorders, self-reported psychiatric diagnoses were also included in the questionnaire, including alcoholism, anxiety, bipolar disorder, depression, fibromyalgia, and schizophrenia.

2.2. Analysis. Analyses were conducted both on the full sample (aged 18 and older) and among the portion of the sample aged 65 years and older. Initial analyses compared those experiencing no residual symptoms to those who experienced at least one residual symptom using chi-square test for categorical variables and independent-samples *t*-tests for continuous variables. The relationship between the severity of residual effects and outcomes was also analyzed using multivariable regression. The multivariable models adjusted for covariates to reduce the likelihood that observed effects of residual symptoms were due to confounding factors. Covariates included gender (male versus female), race/ethnicity, age (continuous), BMI (overweight, obese, and missing versus normal/underweight), household income, comorbidity burden according to CCI, and a variety of psychiatric illnesses, which were found to be associated with residual symptoms during review of bivariate analyses. Models of treatment satisfaction were conducted using the total score from the SATMED-Q and were conducted using maximum likelihood linear regression. Likewise, ratings of disability were approximately normally distributed and also analyzed using linear models. Models of impairments measured by the WPAI were conducted using generalized linear models (GLMs) specifying a negative binomial distribution and a log-link function. All analyses were conducted first in the full sample and repeated in the subsample aged 65 and older.

3. Results

Sample characteristics are presented in Table 1. Respondents were 52 years old on average, 78% were female and 87% were white. Most had their insomnia diagnosed and managed by a general practitioner. Psychiatric comorbidities were common among the sample, with approximately 50% reporting depression and approximately one-third of the sample reporting an anxiety disorder.

Approximately 80% of current users (1,274/1,605) indicated some level of residual symptoms. Those reporting residual symptoms were slightly younger on average, but otherwise there were few demographic characteristics that differed across the presence of residual symptoms (Table 2). However, health characteristics differed according to presence of residual symptoms, with anxiety, depression, schizophrenia, and fibromyalgia all more likely among those with residual symptoms relative to those without residual symptoms, while alcoholism and bipolar disorder were marginally more likely. Psychiatrists were more often the diagnosing and prescribing doctor for those with residual symptoms than those without. The burden of comorbid conditions as represented by the CCI did not differ according to residual symptoms.

Problems with sleep in the prior 7 nights were common in current users of sleep medications. The presence of residual symptoms was associated with one additional day waking up tired/unrested, but not with the number of nights out of the past 7 with trouble falling asleep, staying asleep, or waking before the alarm (Table 3). In contrast, the impact of poor sleep on functioning was greater among those with residual effects, however, as ratings of interference in home management, ability to work, social relationships, and close relationships were all significantly higher among those reporting residual effects. Likewise, those who experienced residual symptoms were less satisfied with their current sleep medication than those who did not experience any residual symptoms (69.2 versus 76.0, $p < 0.001$).

Correlational analyses confirmed that when present, severity of residual symptoms was associated with worse outcomes and lower satisfaction. All residual symptoms were significantly associated with greater ratings of work and activity impairment in bivariate correlations. Difficulty concentrating and drowsiness were particularly burdensome, which were correlated with work and activity impairment $r_s = .46-.49$. Likewise, the severity of difficulty concentrating ($r_s = -.347$, $p < 0.001$) and grogginess ($r_s = -.366$, $p < 0.001$) was most associated with (reduced) satisfaction with sleep medication (data not presented).

Regression analyses confirmed the association between residual symptoms and outcomes. The severity of residual symptoms was associated with lower satisfaction as measured by the SATMED-Q, (Beta = $-.37$, $p < 0.001$). The severity of residual symptoms was also associated with increased residual symptom-related work impairment, including absenteeism (RR = 1.46, 95% CI: 1.34–1.60, $p < 0.001$), presenteeism (RR = 1.12, 95% CI: 1.09–1.14, $p < 0.001$), overall work impairment (RR = 1.13, 95% CI: 1.10–1.15, $p < 0.001$), and impairment in nonwork activities (RR = 1.11, 95% CI: 1.10–1.13, $p < 0.001$). The severity of residual symptoms was also

TABLE 1: Respondent characteristics.

	Current user	
	<i>n</i>	%
Age (Mean, SD)	52.06	12.7
Age (10-year brackets)		
Under 25	27	1.7
25–34	148	9.2
35–44	256	16.0
45–54	429	26.7
55–64	472	29.4
65–74	238	14.8
75 and older	35	2.2
Female	1260	78.5%
Non-white	203	12.6%
Completed college	791	49.3%
Annual household income		
Below \$25k	356	22.2%
\$25–<50k	397	24.7%
\$50–<75k	281	17.5%
\$75k and above	481	30.0%
Decline to answer	90	5.6%
Employed	778	48.5%
BMI (Mean, SD)	26.6	6.6
BMI (categories)		
Underweight	39	2.4%
Normal	544	33.9%
Overweight	472	29.4%
Obese (up to 35)	248	15.5%
Obese (over 35)	200	12.5%
Decline to answer	102	6.4%
Alcohol use	1050	65.4%
Current smoker	387	24.1%
Exercise in previous month	1018	63.4%
Psychiatric comorbidities		
Alcoholism	60	3.7%
GAD or SAD	510	31.8%
Depression	802	50.0%
Schizophrenia	169	10.5%
Bipolar disorder	170	10.6%
Fibromyalgia	221	13.8%
Diagnosing doctor		
General Practitioner/Family Practitioner/Internist	1075	67.0
Psychiatrist	358	22.3
Sleep Specialist	103	6.4
Other	69	4.3
Prescribing doctor		
General Practitioner/Family Practitioner/Internist	1132	70.5
Psychiatrist	363	22.6
Sleep Specialist	33	2.1
Other	77	4.8
Current sleep medication		
Benzodiazepine	331	20.6%
Z-drug	809	50.4%
Antidepressant	335	20.9%
Other	130	8.1%
Still using first sleep medication	341	21.2%

TABLE 2: Respondent characteristics by presence of residual symptoms.

	Residual symptoms				<i>p</i> value
	None (<i>N</i> = 331)		One or more (<i>N</i> = 1,274)		
	<i>n</i>	%	<i>n</i>	%	
Age (Mean, SD)	54.1	12.7	51.5	12.6	0.001
Female	259	78.2%	1001	78.6%	0.898
Non-white	40	12.1%	163	12.8%	0.729
College degree	227	68.6%	862	67.7%	0.750
Annual household income					0.032
Below \$25k	73	22.1%	283	22.2%	
\$25–<50k	71	21.5%	326	25.6%	
\$50–<75k	52	15.7%	229	18.0%	
\$75 k and above	106	32.0%	375	29.4%	
Decline to answer	29	8.8%	61	4.8%	
Employed	153	46.2%	625	49.1%	0.358
BMI (Mean, SD)	27.1	6.8	28.0	6.6	0.048
CCI (Mean, SD)	0.60	1.11	0.77	1.36	0.032*
Alcohol use	224	67.7%	826	64.8%	0.333
Current smoker	75	22.7%	312	24.5%	0.488
Exercise in previous month	207	62.5%	811	63.7%	0.706
Self-report psychiatric diagnoses					
Alcoholism	7	2.1%	53	4.2%	0.081
GAD or SAD	72	21.8%	438	34.4%	<0.001
Depression	128	38.7%	674	52.9%	<0.001
Schizophrenia	23	6.9%	146	11.5%	0.017
Bipolar disorder	26	7.9%	144	11.3%	0.069
Fibromyalgia	31	9.4%	190	14.9%	0.009
Diagnosing doctor for insomnia					0.002
General Practitioner/Family Practitioner/Internist	240	72.5%	835	65.5%	
Psychiatrist	50	15.1%	308	24.2%	
Sleep Specialist	21	6.3%	82	6.4%	
Other	20	6.0%	49	3.8%	
Prescribing doctor					0.005
General Practitioner/Family Practitioner/Internist	246	74.3%	886	69.5%	
Psychiatrist	54	16.3%	309	24.3%	
Sleep Specialist	11	3.3%	22	1.7%	
Other	20	6.0%	57	4.5%	

Note: * indicates Welch's test was used in lieu of parametric *t*-test due to nonhomogeneity of variance.

TABLE 3: Sleep-related trouble according to the presence of residual symptoms.

	Residual symptoms				<i>p</i> value
	None (<i>N</i> = 331)		One or more (<i>N</i> = 1,274)		
	Mean	SD	Mean	SD	
Nights out of 7 with trouble falling asleep	5.1	2.3	5.3	2.0	0.297*
Nights out of 7 with trouble staying asleep	5.4	2.2	5.4	2.2	0.856
Number of days out of 7 waking before alarm	4.6	2.6	4.5	2.5	0.253
Number of days out of 7 waking tired/unrested	4.6	2.4	5.6	1.9	<0.001*
Nights out of 7 with any problem above	6.0	1.5	6.1	1.5	0.891
Sleep problems interfere with home management	3.9	3.0	5.6	2.8	<0.0001
Sleep problems interfere with ability to work	3.1	3.1	4.6	3.2	<0.0001
Sleep problems interfere with social relationships	3.6	3.2	5.3	3.0	<0.0001
Sleep problems interfere with close relationships	3.3	3.2	5.2	3.1	<0.0001

Note: * indicates Welch's test was used in lieu of parametric *t*-test due to nonhomogeneity of variance.

TABLE 4: Respondent characteristics by experience of residual symptoms in respondents aged 65 and older.

	Residual symptoms				<i>p</i> value
	None (<i>N</i> = 78)		One or more (<i>N</i> = 195)		
	<i>n</i>	%	<i>n</i>	%	
Age (Mean, SD)	69.37	4.07	69.72	4.53	0.558
Female	63	80.8%	143	73.3%	0.197
Non-white	4	5.1%	8	4.1%	0.709
Completed college	59	75.6%	145	71.4%	0.466
Annual household income					0.076
Below \$25k	13	16.7%	32	16.4%	
\$25–<50k	13	16.7%	61	31.3%	
\$50–<75k	14	17.9%	34	17.4%	
\$75k and above	26	33.3%	53	27.2%	
Decline to answer	12	15.4%	15	7.7%	
Employed	15	19.2%	33	16.9%	0.651
BMI (categories)					0.968
Underweight	3	3.8%	6	3.1%	
Normal	26	33.3%	66	33.8%	
Overweight	28	35.9%	65	33.3%	
Obese (up to 35)	11	14.1%	34	17.4%	
Obese (over 35)	7	9.0%	19	9.7%	
Refused	3	3.8%	5	2.6%	
Alcohol use	51	65.4%	133	68.2%	0.653
Smokes	13	16.7%	23	11.8%	0.282
Exercise in previous month	43	55.1%	113	57.9%	0.671
Psychiatric comorbidities					
Alcoholic	1	1.3%	6	3.1%	0.397
Anxiety	8	10.3%	45	23.1%	0.016
Depression	18	23.1%	76	39.0%	0.013
Schizophrenia	1	1.3%	33	16.9%	0.000
Bipolar disorder	3	3.8%	5	2.6%	0.570
Fibromyalgia	4	5.1%	31	15.9%	0.016
Diagnosing doctor					0.074
General Practitioner/Family Practitioner/Internist	66	84.6%	142	72.8%	
Psychiatrist	5	6.4%	29	14.9%	
Sleep Specialist	2	2.6%	15	7.7%	
Other	5	6.4%	9	4.6%	
Prescribing doctor					0.264
General Practitioner/Family Practitioner/Internist	82.1%	162	83.1%	82.1%	
Psychiatrist	7.7%	24	12.3%	7.7%	
Sleep Specialist	3.8%	3	1.5%	3.8%	
Other	6.4%	6	3.1%	6.4%	

Note: * indicates Welch's test was used in lieu of parametric *t*-test due to nonhomogeneity of variance.

associated with increases in sleep-related interference on the four domains measured in the BIQ in the regression analyses; home management (Beta = .31, $p < 0.001$), ability to work (Beta = .31, $p < 0.001$), social relationships, (Beta = .32, $p < 0.001$), and close personal relationships (Beta = .30, $p < 0.001$) were all similarly affected.

Analysis of those aged 65 and older also revealed a high proportion (71%; 195 of 273) of current users reporting at least one residual symptom. As in the full sample, the rates

of anxiety, depression, schizophrenia, and fibromyalgia were higher among those with residual symptoms (Table 4). Unlike the full sample, patients aged 65 or older with residual symptoms had higher CCI scores relative to those without residual symptoms.

Results of comparisons of sleep outcomes also mirrored those of the full sample (Table 5). The number of nights with different types of sleep problems were comparable across those with and without residual symptoms except for

TABLE 5: Sleep-related trouble according to the presence of residual symptoms in respondents 65 years and older.

	Residual symptoms				<i>p</i> value
	None (<i>N</i> = 78)		One or more (<i>N</i> = 195)		
	Mean	SD	Mean	SD	
Nights out of 7 with trouble falling asleep	4.6	2.5	5.2	2.1	0.059*
Nights out of 7 with trouble staying asleep	5.4	2.2	5.4	2.2	0.822
Number of days out of 7 wake up before alarm	4.6	2.7	4.3	2.7	0.461
Number of days out of 7 wake up tired/unrested	3.7	2.7	4.9	2.4	0.001*
Nights out of 7 with problem	5.9	1.6	5.8	1.8	0.651
Sleep problems interfere with home management	2.7	2.8	4.6	2.8	<0.001
Sleep problems interfere with ability to work	1.7	2.5	3.0	3.0	0.001*
Sleep problems interfere with social relationships	2.6	3.0	3.9	2.8	0.001
Sleep problems interfere with close relationships	2.5	3.1	3.5	2.9	0.010

Note: * indicates Welch's test was used in lieu of parametric *t*-test due to nonhomogeneity of variance.

days waking up tired or unrested. Also consistent with the full sample, levels of disability due to sleep problems were elevated in those with residual symptoms relative to those without for all four domains measured. Those who experienced at least one residual symptom also had marginally lower satisfaction than those without any residual symptoms (74.7 versus 78.5, $p = 0.057$).

As in the full sample, the expected relationship between residual symptoms and satisfaction with sleep medication was seen in the correlations between satisfaction and ratings of individual residual symptoms (data not presented). Difficulty concentrating was most closely related to satisfaction ($r_s = -.34$, $p < 0.001$). Total residual symptoms and difficulty concentrating were most closely related to sleep medication-related impairment to nonwork activities (both $r_s = .46$, $p < 0.001$).

Regression results demonstrated that total residual symptoms were associated with lower satisfaction with current medication among those aged 65 years and older (Beta = $-.37$, $p < 0.001$). The severity of residual symptoms was also associated with increases in sleep-related interference on home management (Beta = $.30$, $p < 0.001$), social relationships (Beta = $.26$, $p < 0.001$), and close personal relationships (Beta = $.27$, $p < 0.001$). Total residual symptoms were also associated with impairment to nonwork activities on the WPAI (RR = 1.18, 95% CI: 1.11–1.25, $p < 0.001$).

4. Discussion

This study described the relationship between perceived residual sleep medication effects and a wide range of important outcomes for insomnia patients. This was the first study, to our knowledge, to describe the magnitude of the relationship between residual sleep medication effects and this large array of patient-reported outcomes, particularly in a single, large sample. Findings are particularly novel for the older patients, as the literature focuses primarily on what the residual effects are, rather than their correlates, for this demographic group.

Residual medication effects—such as feelings of being drowsy, groggy, or sluggish the next day, difficulty concentrating/remembering, or sleeping too much—were reported by approximately four out of every five individuals currently using prescription sleep medication. Overall, findings showed significant burden experienced by patients reporting residual sleep medication effects relative to those not reporting such effects.

Though patients with and without perceived residual effects suffered a similar number of nights with sleep problems (falling asleep, staying asleep, waking before the alarm, or any problem), the experience of residual effects was associated with an average of one more day per week of “unrestful sleep.” One potential explanation is that the residual effects of the sleep medication itself are responsible for the difference, though this is only speculation; the present analysis was not designed to identify the cause. Patients reporting residual effects were also less satisfied with their medications. Moreover, there were clear relationships between increasingly severe residual symptoms and decreased satisfaction, as well as increasingly severe residual symptoms and greater work and activity impairment, and greater sleep-related interference in home management, ability to work, and social relationships. Though respondents reporting residual effects indicated they experienced more psychiatric symptomatology and other comorbidities than those not experiencing such effects, the relationships between functioning and residual symptom severity remained significant after these and other relevant covariates were accounted for.

Analysis of older patients showed a similar pattern of relationships. Differences between those with and without residual symptoms were only marginal, but the correlation between increasingly severe residual symptoms and decreased satisfaction was of considerable magnitude. Increasing symptom severity corresponded with greater impairment across residual symptom-related nonwork activities, home management, ability to work, and social relationships. These relationships held when relevant covariates were included as well.

In support of prior research, insomnia patients experiencing residual symptoms comprise a group who are under particular strain, even relative to other already-burdened insomnia patients. This study uniquely describes the depth of this strain, which appears to occur across a wide range of domains and is likely affecting patients' global functioning and quality of life. Increasing residual symptom severity appears to affect level of impairment. Regarding financial burden, the strain could be indirectly affecting the work force and healthcare system. As hypothesized, older patients experiencing residual sleep medication effects showed the additional burden of more medical comorbidities. The comorbid conditions could potentially be aggravated or exacerbated by sleep medication side effects.

There are a number of limitations of the current study that should be considered alongside the results. Most importantly, this was an observational study, and the correlational nature of the data collection precludes any causal attribution. Likewise, the cross-sectional design does not allow us to ascertain whether the residual symptoms precede difficulties in home management, ability to work, and so forth, or whether residual symptoms occur in response to a worsening of such problems. Indeed, some residual symptoms, such as grogginess and difficulty concentrating, are also symptoms of insomnia, so some of the residual symptoms reported here may instead be symptoms of inadequately treated insomnia rather than next-day effects of sleep medication or a combination of both inadequate efficacy and medication side effects. Residual effects were self-reported rather than using objective measures of attention, memory, or reaction time. Another study limitation includes the margin of error inherent in any study using self-report measures, though insomnia itself can only be diagnosed via self-report, making self-report vital to this study [11]. Finally, the residual sleep medication effects we reported likely relate to other medical, psychosocial, quality of life, and economic outcomes that we did not measure. We may thus be underestimating the true extent of humanistic and economic burden.

5. Conclusions

Ultimately, patients who experience residual sleep medication effects represent a group with significant impairment of workplace, home, and social life activities; as the perceived severity of the residual symptoms increases, so does the burden. Thus, thorough medical and psychosocial/behavioral assessment of individuals experiencing residual effects is recommended (especially for the elderly). Also, improved management of insomnia would be beneficial. Behavioral and cognitive interventions have essentially no side effects and have been shown to lead to long-lasting, sustained improvements in sleep symptoms and parameters over 6 months to 24 months [28]. However, the degree of sleep medication use in this sample demonstrates that many may prefer, or need, pharmacotherapy for insomnia, highlighting a need for medications with fewer residual symptoms. The development of sleep medications with reduced residual effect profiles will be important for treatment of this patient population.

Conflict of Interests

This study and the preparation of the paper were conducted by Kantar Health with funds from Merck & Co., Inc. Timothy Fitzgerald is an employee of Merck & Co., Inc., and may own Merck & Co., Inc., stock. Jeffrey Vietri is an employee of Kantar Health.

Acknowledgments

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References

- [1] C. M. Morin, M. LeBlanc, M. Daley, J. P. Gregoire, and C. Mérette, "Epidemiology of insomnia: prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors," *Sleep Medicine*, vol. 7, no. 2, pp. 123–130, 2006.
- [2] M. M. Ohayon and C. F. Reynolds III, "Epidemiological and clinical relevance of insomnia diagnosis algorithms according to the DSM-IV and the International Classification of Sleep Disorders (ICSD)," *Sleep Medicine*, vol. 10, no. 9, pp. 952–960, 2009.
- [3] C. M. Morin, L. Bélanger, M. LeBlanc et al., "The natural history of insomnia a population-based 3-year longitudinal study," *Archives of Internal Medicine*, vol. 169, no. 5, pp. 447–453, 2009.
- [4] H. Morphy, K. M. Dunn, M. Lewis, H. F. Boardman, and P. R. Croft, "Epidemiology of insomnia: a longitudinal study in a UK population," *Sleep*, vol. 30, no. 3, pp. 274–280, 2007.
- [5] J. E. Aikens and M. E. Rouse, "Help-seeking for insomnia among adult patients in primary care," *Journal of the American Board of Family Practice*, vol. 18, no. 4, pp. 257–261, 2005.
- [6] N. J. Pearson, L. L. Johnson, and R. L. Nahin, "Insomnia, trouble sleeping, and complementary and alternative medicine: analysis of the 2002 national health interview survey data," *Archives of Internal Medicine*, vol. 166, no. 16, pp. 1775–1782, 2006.
- [7] T. Roth, S. Jaeger, R. Jin, A. Kalsekar, P. E. Stang, and R. C. Kessler, "Sleep problems, comorbid mental disorders, and role functioning in the national comorbidity survey replication," *Biological Psychiatry*, vol. 60, no. 12, pp. 1364–1371, 2006.
- [8] M. T. Smith and J. A. Haythornthwaite, "How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature," *Sleep Medicine Reviews*, vol. 8, no. 2, pp. 119–132, 2004.
- [9] M. Suka, K. Yoshida, and H. Sugimori, "Persistent insomnia is a predictor of hypertension in Japanese male workers," *Journal of Occupational Health*, vol. 45, no. 6, pp. 344–350, 2003.
- [10] A. N. Vgontzas, D. Liao, S. Pejovic et al., "Insomnia with short sleep duration and mortality: the Penn State cohort," *Sleep*, vol. 33, no. 9, pp. 1159–1164, 2010.
- [11] S. L. Schutte-Rodin, L. Broch, D. Buysse, C. Dorsey, and M. Sateia, "Clinical guideline for the evaluation and management of chronic insomnia in adults," *Journal of Clinical Sleep Medicine*, vol. 4, no. 5, pp. 487–504, 2008.

- [12] C. E. Reeder, M. Franklin, and T. J. Bramley, "Current landscape of insomnia in managed care," *American Journal of Managed Care*, vol. 13, supplement 5, pp. S112–S116, 2007.
- [13] C. M. Morin and R. Benca, "Chronic insomnia," *The Lancet*, vol. 379, no. 9821, pp. 1129–1141, 2012.
- [14] A. J. Roth, W. V. Mccall, and A. Liguori, "Cognitive, psychomotor and polysomnographic effects of trazodone in primary insomniacs," *Journal of Sleep Research*, vol. 20, no. 4, pp. 552–558, 2011.
- [15] J. S. Poceta, "Zolpidem ingestion, automatisms, and sleep driving: a clinical and legal case series," *Journal of Clinical Sleep Medicine*, vol. 7, no. 6, pp. 632–638, 2011.
- [16] M.-J. Tsai, Y.-H. Tsai, and Y.-B. Huang, "Compulsive activity and anterograde amnesia after zolpidem use," *Clinical Toxicology*, vol. 45, no. 2, pp. 179–181, 2007.
- [17] A. M. Holbrook, R. Crowther, A. Lotter, C. Cheng, and D. King, "Meta-analysis of benzodiazepine use in the treatment of insomnia," *Canadian Medical Association Journal*, vol. 162, no. 2, pp. 225–233, 2000.
- [18] G. K. Zammit, B. Corser, K. Doghramji et al., "Sleep and residual sedation after administration of zaleplon, zolpidem, and placebo during experimental middle-of-the-night awakening," *Journal of Clinical Sleep Medicine*, vol. 2, no. 4, pp. 417–423, 2006.
- [19] A. Y. Avidan, B. E. Fries, M. L. James, K. L. Szafara, G. T. Wright, and R. D. Chervin, "Insomnia and hypnotic use, recorded in the minimum data set, as predictors of falls and hip fractures in Michigan nursing homes," *Journal of the American Geriatrics Society*, vol. 53, no. 6, pp. 955–962, 2005.
- [20] S. Wilson and S. Argyropoulos, "Antidepressants and sleep: a qualitative review of the literature," *Drugs*, vol. 65, no. 7, pp. 927–947, 2005.
- [21] J. C. Verster and T. Roth, "Gender differences in highway driving performance after administration of sleep medication: a review of the literature," *Traffic Injury Prevention*, vol. 13, no. 3, pp. 286–292, 2012.
- [22] J. Glass, K. L. Lanctôt, N. Herrmann, B. A. Sproule, and U. E. Busto, "Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits," *The British Medical Journal*, vol. 331, no. 7526, article 1169, 2005.
- [23] S. D. Berry, Y. Lee, S. Cai, and D. D. Dore, "Nonbenzodiazepine sleep medication use and hip fractures in nursing home residents," *JAMA Internal Medicine*, vol. 173, no. 9, pp. 754–761, 2013.
- [24] M. C. Reilly, A. S. Zbrozek, and E. M. Dukes, "The validity and reproducibility of a work productivity and activity impairment instrument," *Pharmacoeconomics*, vol. 4, no. 5, pp. 353–365, 1993.
- [25] R. C. Kessler, C. Coulouvrat, G. Hajak et al., "Reliability and validity of the brief insomnia questionnaire in the America Insomnia Survey," *Sleep*, vol. 33, no. 11, pp. 1539–1549, 2010.
- [26] M. A. Ruiz, A. Pardo, J. Rejas, J. Soto, F. Villasante, and J. L. Aranguren, "Development and validation of the 'treatment satisfaction with medicines questionnaire' (SATMED-Q)," *Value in Health*, vol. 11, no. 5, pp. 913–926, 2008.
- [27] M. E. Charlson, P. Pompei, K. L. Ales, and C. R. MacKenzie, "A new method of classifying prognostic comorbidity in longitudinal studies: development and validation," *Journal of Chronic Diseases*, vol. 40, no. 5, pp. 373–383, 1987.
- [28] O. C. Ioachimescu and A. A. El-Solh, "Pharmacotherapy of insomnia," *Expert Opinion on Pharmacotherapy*, vol. 13, no. 9, pp. 1243–1260, 2012.

REVIEW**Cannabis, Pain, and Sleep: Lessons from Therapeutic Clinical Trials of *Sativex*[®], a Cannabis-Based Medicine**by **Ethan B. Russo**^{*a)b)}, **Geoffrey W. Guy**^{a)}, and **Philip J. Robson**^{a)}^{a)} *GW Pharmaceuticals*, Porton Down Science Park, Salisbury, Wiltshire SP4 OJQ, U.K.^{b)} *GW Pharmaceuticals*, 20402 81st Avenue SW, Vashon, WA 98070, USA

(phone: +1-206-408-7082; fax: +1-866-234-7757; e-mail: erusso@gwpharm.com)

Cannabis sativa L. has been utilized for treatment of pain and sleep disorders since ancient times. This review examines modern studies on effects of Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD) on sleep. It goes on to report new information on the effects on sleep in the context of medical treatment of neuropathic pain and symptoms of multiple sclerosis, employing standardized oromucosal cannabis-based medicines containing primarily THC, CBD, or a 1:1 combination of the two (*Sativex*[®]). Sleep-laboratory results indicate a mild activating effect of CBD, and slight residual sedation with THC-predominant extracts. Experience to date with *Sativex* in numerous Phase I–III studies in 2000 subjects with 1000 patient years of exposure demonstrate marked improvement in subjective sleep parameters in patients with a wide variety of pain conditions including multiple sclerosis, peripheral neuropathic pain, intractable cancer pain, and rheumatoid arthritis, with an acceptable adverse event profile. No tolerance to the benefit of *Sativex* on pain or sleep, nor need for dosage increases have been noted in safety extension studies of up to four years, wherein 40–50% of subjects attained good or very good sleep quality, a key source of disability in chronic pain syndromes that may contribute to patients' quality of life.

Introduction. – Sleep disorders are important syndromes in modern medicine that include parasomnias, or sleep-disruptive events, as well common associated afflictions such as snoring and sleep apnea. The most common disorder is insomnia, or lack of sleep, said by the *National Institute of Neurological Disorders and Stroke* to afflict 60 million Americans [1]. Insomnia is a major risk factor for associated morbidity even in the absence of illness, and is associated with markedly increased prevalence of depression, anxiety, absenteeism [2], accidents [3], and utilization of health care resources [4]. Sleep disruption itself, as in shift work in nurses, may contribute notably to anxiety and functional bowel disorders [5]. When such sleep disturbances occur secondary to pain, they can be termed '*symptomatic insomnia*'. Pain at night at least three times a week was identified as a significant factor in excessive daytime sleepiness in older adults [6]. When sleep disturbance accompanies chronic pain or disease, attendant treatment becomes increasingly problematic. Despite the prevalence and pervasiveness of symptomatic insomnia, very few studies have addressed it, particularly with respect to possible effects of analgesics on sleep. For example, use of non-steroidal anti-inflammatory drugs may be associated with gastroesophageal reflux [7] that itself aggravates insomnia [8].

Fewer studies yet have employed modern methods of electroencephalography (EEG) or polysomnography to assess sleep disorders associated with chronic pain. Results of recent investigations are sobering, as formal sleep monitoring of patients with advanced cancers demonstrated that opioid treatment and pain disrupted nocturnal sleep, prolonged sleep latency, and limited attainment of sleep stages 3 and 4 as well as rapid eye movement sleep [9]. Further investigation indicated that such sleep disturbances were attributable to opioid treatment itself, which contributed to depression and even enhanced pain [10]. In light of such data, it is clear that new approaches to chronic pain and resultant sleep disorder are necessary.

Cannabis sativa L. and its derivatives have been known since ancient times for their analgesic, soporific, and hypnotic effects. While mentioned frequently as beneficial to sleep in a variety of pathological conditions in 19th-century sources on Indian hemp [11], modern studies on cannabinoids and their therapeutic effects on sleep have received little attention in modern medical literature until the last few years. As will be noted, these are indications for which standardized cannabis-based medicine promises palliation and symptomatic relief that may contribute greatly to patients' global impressions and subjective sense of relief of their condition.

The primary psychoactive ingredient of cannabis is Δ^9 -tetrahydrocannabinol (THC), many of whose actions are mediated *via* the CB₁ G-protein coupled receptors that cluster in nociceptive areas of the brain [12], spinal cord [13][14], and peripheral nervous system [15] (see [16] for an excellent review). THC Activity mimics that of the natural endocannabinoids, anandamide (AEA, arachidonylethanolamide) and 2-arachidonylglycerol (2-AG), that are likewise partial agonists on the CB₁ receptor, that modulate pain responses in integrative centers such as the periaqueductal grey matter [17] and pain in relation to stress [18]. Another important phytocannabinoid, the non-psychoactive cannabidiol (CBD), is not only an analgesic, anti-inflammatory, and antioxidant in its own right [19–21], but it is also reported to allay various THC adverse effects including sedation, tachycardia, and anxiety [22]. Recent work has demonstrated that CBD antagonizes tissue necrosis factor alpha (TNF- α) in a rodent model of rheumatoid arthritis [23], and enhances adenosine receptor A2A signaling *via* inhibition of an adenosine transporter [24], suggesting an important therapeutic role in various inflammatory and chronic pain states.

Additional cannabis components including terpenoids and flavonoids also have analgesic properties that may be significant [25]. Historical and scientific aspects of cannabinoids and pain have been described for migraine [26], obstetrics and gynecology [27], and gastroenterological conditions [28]. A clinical endocannabinoid deficiency has been hypothesized in relation to migraine, fibromyalgia, and idiopathic bowel syndrome [29].

In the current review, we will examine modern studies on effects of THC and CBD on sleep, and then report new information on the effects of cannabis-based medicines on sleep as a secondary outcome measure in the context of randomized clinical trials of medical treatment of chronic pain states, including neuropathic pain (NP), symptoms of multiple sclerosis (MS), and rheumatoid arthritis.

Clinical Studies of Cannabinoids and Sleep. – The soporific qualities of cannabis were noted in the ancient Indian *ayurveda* tradition [30]. Subsequently, the great

taxonomist *Linnaeus* recognized cannabis as *narcotica* and *anodyna* in his *Materia Medica* in the 18th century [31] (p. 214). *William B. O'Shaughnessy* reintroduced cannabis to Western medicine from India in the 19th century [32], wherein it produced sleep and pain reduction for victims of rheumatism and many other conditions. Benefits on sleep were noted in various pain states [11] throughout the 19th and early 20th century, when cannabis medicines subsequently fell from common medical usage due to lack of standardization and daunting problems with dosing and quality control.

Scientific study of cannabinoids entered the modern era in the early 1960s with the isolation of THC [33]. Early studies revealed that THC reduced sleep latency in normal and insomniac subjects, and caused some suppression of slow wave sleep (Stages 3 and 4) [34], often with a residual 'hangover' effect the next day [35]. No formal studies of cannabinoids to date have included electroencephalography or polysomnography in symptomatic conditions or chronic pain states.

In a recent case report [36], treatment with *Marinol*[®] (dronabinol, synthetic THC) effectively reversed serious insomnia in three patients afflicted with intractable pruritus associated with cholestatic liver disease. Similarly, in a limited trial of *Marinol*, 2.5 mg at night in five dementia patients, a reduction was observed in nocturnal motor activity ($p = 0.028$) [37].

A series of experiments with cannabidiol performed in Brazil were summarized in 1981 [38], with observations based on subjective sleep assessments. Of two subjects taking CBD 300 mg twice a day (BID) for 2 d, one reported having slept more heavily, but no performance abnormalities were evident. Ten more subjects took 200 mg CBD vs. placebo on four separate occasions with no significant differences in subjective functioning, or level of alertness. Two of four subjects taking CBD, 10 mg BID for 20 d, complained of isolated episodes of daytime somnolence on rare occasions. Another experiment compared placebo to CBD, 3 mg/kg/d divided BID in eight subjects. One reported somnolence for a week, another for the entire 30 d, and a third reported improvement in baseline insomnia.

Subsequently, this group assessed 15 subjects with 40, 80, and 160 mg oral doses of CBD as a hypnotic vs. nitrazepam, 5 mg, and placebo in a double-blind randomized trial. This low dose of benzodiazepine and lower dose of CBD produced little effect on sleep. The highest CBD dose, however, seemed to extend sleep and reduce episodic waking in 10/15 subjects subjectively, while also reducing dream recall. No hangover symptoms were noted.

Cannabinoid Effects on Brain Chemistry in Sleep. – The key role of the endogenous cannabinoid system in regulation of sleep–wake cycles was suggested by the finding that the CB₁ antagonist/inverse agonist SR 141716A produces arousal in rats at the expense of slow-wave sleep [39]. This was further highlighted by the finding that the endocannabinoid anandamide (AEA) seems to mediate sleep induction and interacts with oleamide in this regard [40]. Subsequently, a Japanese group demonstrated the inhibition of serotonin and ketanserin (5-HT_{2A} antagonist) binding to the 5-T receptors by AEA [41]. A mild but similar response has recently been demonstrated for CBD [42], and cannabis terpenoids [43], suggesting a possible synergy with the CB₁ agonist, THC. Certain terpenoid components of cannabis are sedating in their own right (reviewed in [44], particularly terpineol [45]).

Recently, CBD was shown to inhibit uptake of AEA, and weakly inhibit its hydrolysis [46], making it, in effect, an inducer of AEA function, and suggesting a modulatory role for this agent in sleep. Additionally, a functional role for endocannabinoids in regulation of respiratory stability in sleep to prevent sleep apnea has been suggested [47]. Finally, it has recently been demonstrated that CBD administered intracerebroventricularly in rats increased wakefulness in the lights-on period, and increased enhancement of c-FOS expression in hypothalamus and dorsal raphe nucleus [48], supporting a clinical alerting effect for this agent [22], as discussed below.

New Data on Sleep Modulation with Cannabis-Based Medicine Extracts (CBMs). – *GW Pharmaceuticals* received a license from the *British Home Office* in 1998 to cultivate cannabis and extract it as a standardized botanical drug substance for formulation into finished pharmaceutical products. Early indications have focused on multiple sclerosis (MS) and chronic pain, especially neuropathic, or associated with cancer and rheumatoid arthritis. Chemovars of cannabis were selected *via Mendelian* genetics to express one predominant phytocannabinoid [49][50]. Cloned plants undergo liquid CO₂ extraction to produce botanical drug substances that contain predominantly THC (*Tetranabinex*®), CBD (*Nabidiolex*®), or a 1:1 combination of the two (*Sativex*®; *Fig. 1*) [51][52]. *Sativex* is administered oromucosally *via* a pump-action spray with each 100- μ l pump-action actuation providing 2.7 mg of THC, 2.5 mg of CBD plus other phytocannabinoids, terpenoids, and phytosterols [25], in a base of 50% EtOH and 50% propylene glycol with 0.05% peppermint flavoring. Pharmacokinetic data on this material is available from recent publications [53]. The preparation has onset of activity in 15–40 min, which allows patients to titrate dosing requirements according to pain levels or other symptoms with an acceptable profile of adverse events.



Fig. 1. *Sativex oromucosal cannabis based medicine* (photo: *Ethan Russo*, 2003)

A total of 1000 patient years of *Sativex* exposure in over 2000 experimental subjects has been amassed in Phase-II and -III clinical trials. A slight majority of subjects had no previous recreational or medicinal cannabis exposure, but comparative efficacy results have been identical in cannabis-experienced and cannabis-naïve cohorts with no evidence of inadequacy of subject blinding [54][55]. Patients are generally able to find a stable dose at which they obtain therapeutic relief without unwanted psychoactive effects. All randomized controlled trials (RCTs) were performed with *Sativex* added as an adjunct to existing drug regimens in patients with intractable symptoms, *i.e.*, patients considered treatment-resistant and remained on best available analgesic therapy and hypnotic medication, if prescribed. A concerted effort has been made in this review to include data from all available *Sativex* clinical trials; no negative data were excluded.

Sativex was approved in June 2005 for marketing as a prescription medicine in Canada under a *Notice of Compliance with Conditions* (NOC/c) for central neuro-pathic pain in multiple sclerosis (MS). An *Investigational New Drug* (IND) application to study *Sativex* in intractable cancer pain patients in the USA was approved by the FDA in January 2006. Two independent reviews of *Sativex* have recently been published [56][57].

The effects of oromucosal high-THC extract (*Tetranabinex*®), 15 mg, and THC-CBD extract doses of 5 and 15 mg of THC-equivalent were assessed by *Nicholson et al.* in eight subjects with respect to nocturnal sleep, early morning performance, memory, and residual sleepiness in a double-blind placebo-controlled four-way cross-over study with EEG monitoring [58]. While the THC extract, 15 mg, alone produced little effect on sleep architecture, sleep latency was reduced, memory was impaired, and residual sleepiness and mood changes were observed ($p < 0.05$). Both dose levels of combined THC-CBD extract decreased Stage 3 sleep ($p < 0.05$) over placebo, and the 15-mg doses increased wakefulness ($p < 0.05$) compared to 5-mg doses. The 5-mg doses of THC-CBD extract actually produced faster reaction times on the digit recall test ($p < 0.05$) over placebo. The authors noted that whereas impaired memory was observed the next day when 15-mg THC extract was given alone overnight, there were no such effects when THC was concomitantly accompanied by 15 mg of CBD, as in *Sativex*. Conclusions were that THC was sedative, while, in contrast, the presence of CBD was alerting, tended to counteract THC adverse effects on cognition, and impaired wakefulness.

In subsequent Phase-II and -III clinical trials, sleep quality was assessed with questionnaires completed by clinical trial subjects. Visual Analogue Scales (VASs) and Numerical Rating Scales (NRSs) are familiar instruments to many clinicians and have traditionally been used to quantify patient-rated subjective experiences. The two types of scale have similar sensitivity and reliability, but NRS is generally preferred by patients for ease of use. NRS and VAS are well-established and validated for the measurement of pain [59]. As is the case with pain, there is no objective gold standard by which to quantify the quality and quantity of sleep in patients participating in clinical trials. For this reason, most of the studies included in this review utilized NRSs or VASs to measure sleep and sleep disturbance. For example, *Wade et al.* [60] used VASs attached to the following questions: ‘How was your quality of sleep last night?’/‘How much sleep did you get last night?’/‘How did you feel when you awoke this morning?’ The anchors at each extremity of the 10-cm line were ‘best imaginable’ and ‘worst

imaginable for the first two questions, and *totally refreshed* or *totally unrefreshed* for the third. As an example of NRS, Rog *et al.* [61] used an 11-box (0–10) scale attached to the following instruction: ‘On a scale of 0–10 please indicate how your nerve pain disrupted your sleep last night. Please tick one box only’. The anchors were ‘did not disrupt sleep’ and ‘completely disrupts (unable to sleep due to pain)’. Such measures appear to have good face validity.

These and other studies of cannabis-based medicines on pain and sleep are summarized in the *Table*.

In a Phase-II study in 24 patients with intractable neurogenic symptoms including MS and chronic pain, *Tetranabinex*, *Nabidiolex*, and *Sativex* were tested in a double-blind-*N*-of-1 RCT vs. placebo by Wade *et al.* [66]. Significant improvement was seen with both *Tetranabinex* and *Sativex* on pain (especially neuropathic) ($p < 0.05$), but *post-hoc* analysis showed symptom control was best with *Sativex* ($p < 0.0001$), with slightly less intoxication than with THC-predominant extract. *Sativex* significantly improved sleep quality ($p = 0.041$; Study GWN19902; *Fig. 2*) [66]. The authors noted that, compared to placebo, the CBD-predominant extract significantly improved pain, the THC-predominant extract yielded significant improvements in pain, muscle spasm, spasticity, and appetite, and combined THC:CBD extracts (*Sativex*) significantly improved muscle spasm and sleep. They also observed that the visual analogue scale for *Sativex* was significantly improved over baseline for 20 subjects in the sleep category ($p < 0.05$). Of particular note in this trial was the confirmation of the CBD component as alerting, while high THC extract (*Tetranabinex*) improved sleep parameters (although not statistically significantly over placebo in this trial), while the combination of the two (*Sativex*) improved sleep synergistically.

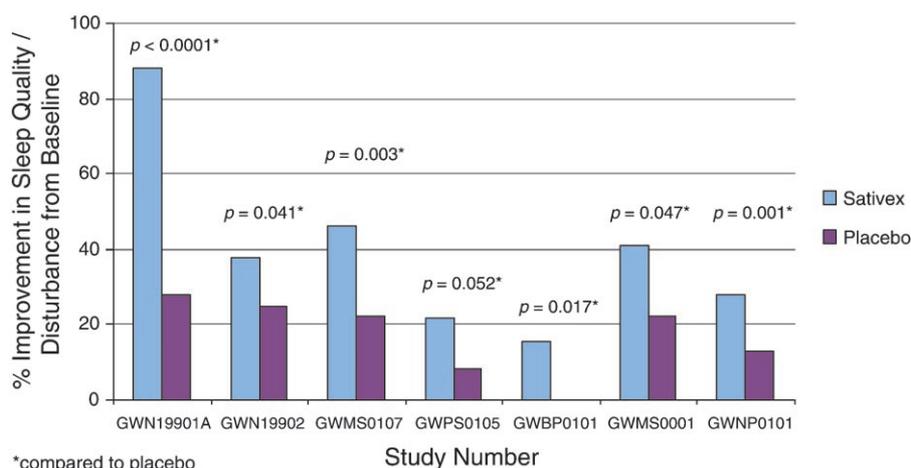


Fig. 2. Compendium of results of *Sativex* on sleep in earlier Phase II–III RCTs in multiple sclerosis (MS) and intractable chronic pain

In a Phase-II double-blind crossover *N*-of-1 study of intractable chronic pain in 34 subjects by Notcutt *et al.* [67], visual analogue scales for pain were significantly improved for *Tetranabinex* and *Sativex* extracts over placebo ($p < 0.001$). *Sativex*

produced best results for pain in MS subjects ($p < 0.0042$). Marked improvement was observed on sleep duration ($p = 0.0001$) and quality ($p = 0.0001$; Study GWN19901A; Fig. 2). The authors commented that *Sativex*, while having little effect on the recorded sleep hours, rather produced marked changes in reported sleep quality from the ‘poor’ or ‘fair’ to ‘good’ categories. The sleep quality measure represented a global assessment by the subject of sleep duration, depth, and relative degree of sleep disruption. Finally, they posited that improvement of sleep by the drug might prove to be one of its major benefits in chronic pain and MS.

In a Phase-III randomized placebo-controlled clinical trial in central neuropathic pain due to MS over 5 weeks in 66 patients by *Rog et al.*, subjects showed mean NRS analgesia favoring *Sativex* over placebo ($p = 0.009$), and significant benefit of *Sativex* over placebo was observed in sleep disturbance ($p = 0.003$) [61] (Study GWMS0107; Fig. 2).

In another Phase-III RCT in intractable pain in 79 subjects with MS, diabetic neuropathy, or other conditions by *Notcutt et al.* [72], the *Sativex* cohort utilized escape analgesia a mean of 20.57% of days vs. 50.12% for placebo ($p = 0.002$). Sleep disturbance was also reduced by *Sativex* vs. placebo (Study GWPS0105; Fig. 2), with a treatment difference favoring the former ($p = 0.045$).

In a Phase-III double-blind placebo-controlled trial of peripheral neuropathic pain with allodynia in 125 subjects by *Nurmikko et al.* [73], *Sativex* produced highly statistically significant improvements in pain levels ($p = 0.004$) and dynamic allodynia ($p = 0.042$). Marked reductions in sleep disturbance were observed ($p = 0.001$; Study GWNP0101; Fig. 2) [73].

In the largest clinical study of brachial plexus avulsion and central neuropathic pain to date by *Berman et al.* [68] in 48 subjects in a double-blind cross-over design assessing oromucosal *Tetranabinex*, *Sativex*, and placebo, comparable benefits were noted in Box Scale-11 pain scores with *Tetranabinex* ($p = 0.002$) and *Sativex* extracts ($p = 0.005$). Sleep disturbance scores favored *Sativex* over placebo ($p = 0.017$) [68] (Study GWBP0101; Fig. 2), with sleep quality scores also favoring *Sativex* ($p = 0.019$).

In another Phase-III RCT focusing on mixed neurogenic symptoms in MS by *Wade et al.* [60], the greatest improvement following *Sativex* was noted in spasticity ($p = 0.001$). Subjects also demonstrated benefit on sleep disturbance ($p = 0.047$; Study GWMS0001; Fig. 2). From this cohort, 137 patients elected to continue on *Sativex* in safety-extension (SAFEX) studies [74]. Rapid reductions were noted in the first twelve weeks in pain VAS in 47 affected patients with sustained improvements for more than one year. During that time, there was no escalation of dose indicating an absence of tolerance to analgesic or other therapeutic benefits of the preparation. Similarly, no withdrawal syndrome (as defined by *Budney et al.* [75]) was noted in a subset of 25 patients who voluntarily stopped the medicine abruptly. Upon resumption, benefits resumed at the prior established dosages. Improvements in sleep were also maintained [74].

Additional data from patients with central and peripheral neuropathic pain who completed these RCTs have been collected in a second SAFEX study of some 507 subjects taking *Sativex* for at least one, and up to four years. These data confirm the continued efficacy of *Sativex* in maintaining improvements in subjective sleep parameters. As in the prior SAFEX in MS subjects with mixed symptoms [74], no

Table. *Clinical Studies of Cannabis Based Medicines on Pain and Sleep*

Drug	Clinical indication	Subject number (N)	Trial duration	Results/reference
Cannabis (smoked)	HIV neuropathy	50	5 days	> 30% pain reduction vs. placebo ($p=0.04$), sleep NA [62]
<i>Cannador</i>	Spasticity in MS	419	15 weeks	Improvement over placebo in subjective pain associated with spasm ($p=0.003$), sleep ($p=0.025$) [63]
<i>Cannador</i>	Post-herpetic neuralgia	65	4 weeks	No benefit observed on pain, sleep NA [64]
<i>Cannador</i>	Post-operative pain	30	Single doses, 1 day each	Decreasing pain intensity with increasing dosage ($p=0.01$). Sleep NA formally. One complaint of sleep disturbance [65]
<i>Sativex</i>	Neurogenic pain	20	Series of 2-week N-of-1 crossover blocks	Improvement with <i>Tetranabinex</i> and <i>Sativex</i> on VAS pain vs. placebo ($p<0.05$), symptom control best with <i>Sativex</i> ($p<0.0001$). <i>Sativex</i> improved sleep quality ($p=0.041$) [66]
<i>Sativex</i>	Chronic intractable pain	24	12 weeks, series of N-of-1 crossover blocks	VAS pain improved over placebo ($p<0.001$) especially in MS ($p<0.0042$). Sleep duration and quality both improved ($p=0.0001$) [67]
<i>Sativex</i>	Brachial plexus avulsion	48	6 weeks in 3 two-week crossover blocks	Benefits noted in Box Scale-11 pain scores with <i>Tetranabinex</i> ($p=0.002$) and <i>Sativex</i> ($p=0.005$) over placebo. <i>Sativex</i> improved sleep disturbance ($p=0.017$) and sleep quality scores ($p=0.019$) [68]
<i>Sativex</i>	Central neuropathic pain in MS	66	5 weeks	Numerical Rating Scale (NRS) analgesia improved ($p=0.009$), sleep disturbance ($p=0.003$) vs. placebo [61]
<i>Sativex</i>	Peripheral neuropathic pain	125	5 weeks	Improvements in NRS pain levels ($p=0.004$), dynamic allodynia ($p=0.042$), sleep disturbance ($p=0.001$) vs. placebo [69]
<i>Sativex</i>	Rheumatoid arthritis	56	5 week	Improvements over placebo morning pain on movement ($p=0.044$), morning pain at rest ($p=0.018$), DAS-28 ($p=0.002$), and SF-MPQ pain at present ($p=0.016$), sleep quality ($p=0.027$) [70]

Table (cont.)

Drug	Clinical indication	Subject number (N)	Trial duration	Results/reference
Sativex	Pain after spinal injury	117	10 days	NSD in sleep disturbance and NRS pain scores, but improved Brief Pain Inventory ($p=0.032$) and Patients Global Impression of Change ($p=0.001$, odds ratio 3.4).
Sativex	Intractable cancer pain	177	2 weeks	Improvements in NRS analgesia vs. placebo ($p=0.0142$), <i>Tetranabinex</i> NSD. Sleep quality NSD [71]
Sativex	Intractable lower urinary tract symptoms in MS	135	8 weeks	Improvement in bladder severity symptoms ($p=0.001$) and nocturia episodes ($p=0.01$) over placebo.

dose escalation over time was necessary to maintain efficacy, supporting a lack of tolerance to this clinical benefit. Specifically, in an initial combined cohort of 287 subjects with central or peripheral neuropathic pain (Fig. 3), ca. 40% of subjects attained good-to-very-good sleep quality with maintenance of up to two years. Fewer than 20% of subjects had less than satisfactory results in their assessments of sleep quality.

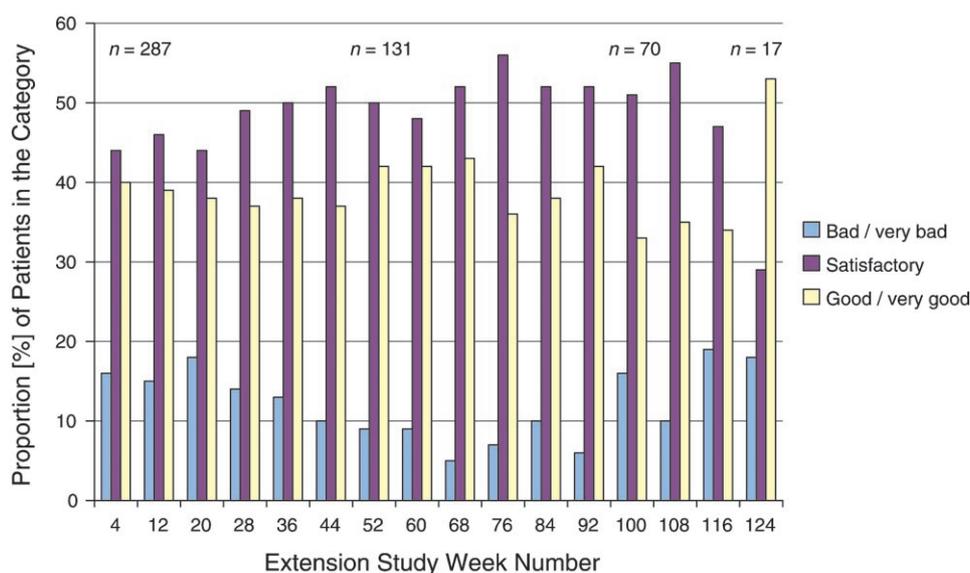


Fig. 3. Cumulative data on sleep disturbances (sleep quality scores) in a long-term safety-extension (SAFEX) study of central and peripheral neuropathic pain patients treated with Sativex (Study GWEXT0102)

An examination of adverse event profiles from the two SAFEX studies (137 and 537 subjects, resp.) reveals that complaints attributed to poor sleep or residual fatigue are infrequent after regular use of *Sativex* (Fig. 4).

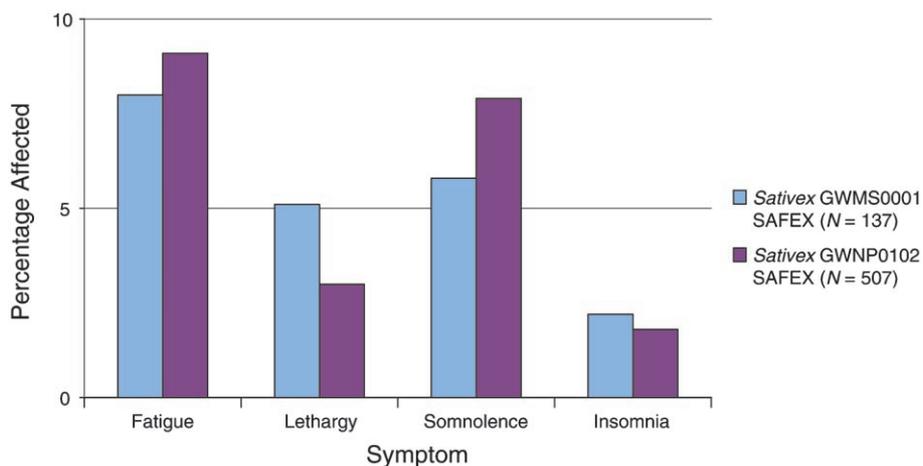


Fig. 4. Graph of fatigue and other adverse events attributable to sedation or sleep disturbance in safety-extension studies of mixed symptoms of multiple sclerosis (MS) (SAFEX GWMS0001, N = 137), and peripheral and central neuropathic pain (SAFEX GWNP0102, N = 507) taking *Sativex* for greater than one and up to four years. Rates of associated complaints are all less than 10%.

In a Phase-II double-blind, randomized placebo-controlled five-week study of 56 rheumatoid arthritis patients with *Sativex* by Blake *et al.* [70], employing nocturnal treatment only, subjects received a maximum of 6 sprays each evening (16.2 mg THC + 15 mg CBD). In the final treatment week, many study measures favored *Sativex* over placebo: morning pain on movement ($p=0.044$), morning pain at rest ($p=0.018$), 28-joint disease activity score (DAS-28; $p=0.002$), and Short Form *McGill* Pain Questionnaire (SF-MPQ) pain at present ($p=0.016$). Sleep quality favored *Sativex* over placebo ($p=0.027$) (Fig. 5, a).

Results of a Phase-III study ($N=177$) comparing *Sativex*, *Tetranabinex*, and placebo in intractable pain due to cancer unresponsive to opiates by Johnson and Potts [71] demonstrated that *Sativex* produced highly statistically significant improvements in analgesia ($p=0.0142$), while *Tetranabinex* was not significantly different from placebo, suggesting that the presence of CBD in the *Sativex* preparation contributed to pain control. Sleep quality in this study was not significantly improved over placebo, perhaps due to its short duration of only three weeks.

Similarly, in a Phase-II study of neuropathic pain after spinal injury, whereas no significant difference was noted in the primary outcome measure of average daily pain due to a large placebo response, the Brief Pain Inventory (BPI) did improve ($p=0.032$), as did the Patients Global Impression (PGI) of change ($p=0.001$, odds ratio 3.4). No changes in sleep over placebo were noted in this brief ten-day trial (unpublished findings).

In a Phase-III RCT of MS patients with intractable lower urinary tract symptoms and frequent accompanying pain in 135 subjects, *Sativex* produced a significant

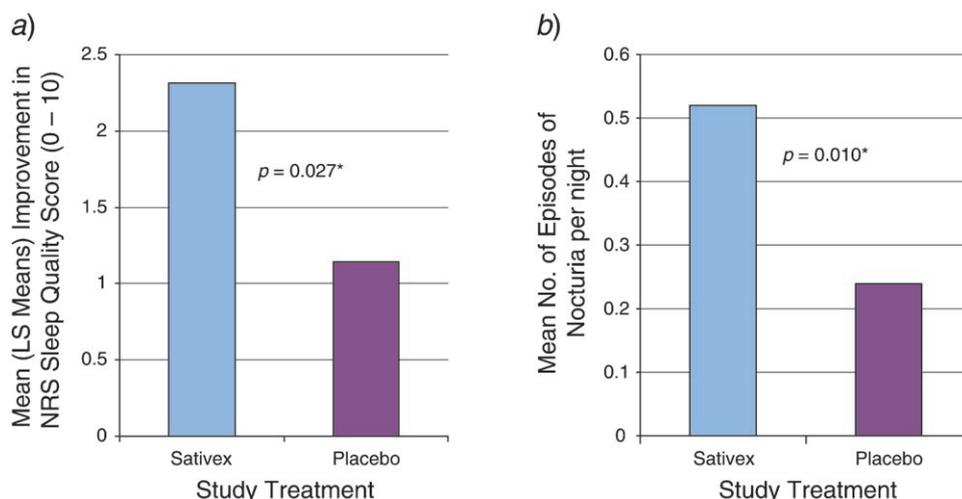


Fig. 5. a) Effect of Sativex vs. placebo on rheumatoid arthritis sleep quality GWCR1016 ($N=58$; 0–10 NRS, 0=‘very good’ and 10=‘very bad’). b) Effect of Sativex vs. placebo on nocturia in intractable lower urinary tract symptom patients with multiple sclerosis ($N=135$).

improvement over placebo in bladder symptom severity ($p=0.001$) and in nocturia episodes ($p=0.010$) affecting sleep (Fig. 5,b) (Fowler et al., GW Pharmaceuticals data on file, manuscript in preparation).

Common Adverse Events (AE) of *Sativex* acutely in RCTs have included complaints of bad taste, oral stinging, dry mouth, dizziness, headache, nausea, or fatigue, but do not generally necessitate discontinuation, and proved less common over time. Cumulative subject withdrawals from the RCTs secondary to AEs attributable to *Sativex* have occurred in 10.7% of all subjects, and in 10.8% of MS subjects (data on file, GW Pharmaceuticals, May 24, 2006). Figures ranged from 12.5% in the first Phase-II trial [60], while 0% of *Sativex* subjects withdrew due to attributable AEs in studies of lower urinary tract symptoms in MS [76] and brachial plexus avulsion [68].

Placebo-controlled trials have also been conducted with an oral plant-derived cannabis-based medicine, *Cannador*, which contains variable THC:CBD ratios [22]. This was examined in a large trial alongside *Marinol* (synthetic THC) and placebo in MS patients (Table). In neither the acute trial (CAMS) reported by Zajicek et al. [63], nor its 12-month long-term follow-up [77], were significant improvements noted in sleep with *Cannador* or *Marinol*. These data would support the proposition that benefits of cannabis-based medicines on sleep in the context of symptomatic treatment may be specific to a preparation’s formulation and/or delivery system, and the improvement with one preparation cannot necessarily be extrapolated to another. Another study of *Cannador* in post-operative pain (Table) showed decreased pain with increasing dosage, but sleep was not assessed formally (NA) [65]. One subject noted sleep disturbance. Finally, *Cannador* was utilized in a four-week study of post-herpetic neuralgia (Table), but no benefit was observed on pain, and sleep was NA formally [64].

Results are recently available from the first RCT of smoked cannabis on pain, in sensory neuropathy due to HIV/AIDS or its treatment (*Table*) [62]. A greater than 30% reduction in pain *vs.* placebo was noted in this five-day trial, but sleep effects were not reported. An additional study is planned in California to assess effects of cannabis on sleep disturbance in similarly affected patients (http://www.cmc.ucsd.edu/geninfo/drummond_abs.htm). The FDA has recently published guidelines for botanical medicines that mandate parameters required for *New Drug Approval* [78]. The difficulties inherent in standardizing herbal cannabis, and pulmonary issues associated with its inhalation [79], make it unlikely that regulatory approval would be attainable in most nations of the world [54].

No head-to-head trials of *Sativex vs.* smoked cannabis have been performed, but a comparison of AE profiles from self-selected SAFEX study subjects on *Sativex* with those of smoked-cannabis patients utilizing standardized cannabis in government programs in Canada [80] and the Netherlands [81][82] supports the concept that *Sativex* was much better tolerated, especially with respect to mental status and cognitive issues [54].

Discussion. – Chronic pain, neurological illness, and sleep disorders are clearly comorbid conditions. Upwards of 80% of MS patients suffer from debilitating fatigue symptoms and complain of significant sleep disturbance. Additionally, chronic pain accompanies MS in up to 60% in some surveys, with a citation of 48% in a recent study [83], further compromising the ability of patients to attain rest. *Tachibana et al.* [84] noted that such problems in MS arise from legion sources: pain, spasticity, muscle spasm, restless legs syndrome, myoclonus, and lower urinary tract symptoms, resulting in sleep disturbance in 80% of 28 subjects. It was felt by these authors that these problems were rarely addressed therapeutically. MS may also be associated with sleep apnea, a condition that has recently been demonstrated to respond favorably to treatment with THC in an animal model [47].

A recent study of sleep and fatigue in 60 MS subjects is quite germane [85], with over half noting difficulty with sleep disturbance at least two nights per week. Fatigue and excessive daytime sleepiness affected 64 and 32% of subjects, respectively. Those problems correlated best to difficulties with middle-of-the-night insomnia that subjects attributed most often to pain/discomfort (21.7%) or nocturia symptoms (72.5%). These symptoms were improved by *Sativex* treatment in the above discussed RCTs. Comparison of rates of fatigue, lethargy, somnolence, and insomnia in *Sativex* SAFEX subjects (*Fig. 4*) supports very remarkable amelioration compared to MS patients in the *Stanton* study [85], many of whom were already taking pharmacotherapy for such symptoms. The authors of the latter study specifically recommended symptomatic treatment of pain and nocturia as strategies to minimize sleep disturbance and its diurnal sequelae.

Similar sleep complaints affect patients with other etiologies of neuropathic pain. A current review article strongly suggested treatment of chronic pain with agents that concomitantly improve sleep [86]. A survey of 173 adults with neuropathic pain reported significantly higher rates of sleep disturbance and daytime somnolence *vs.* controls [87], with improvement after institution of specific treatment. Unfortunately, sleep disturbance continued in 43% of 140 subjects suffering from diabetic neuropathy despite treatment [88].

In a recent review [89], the authors state, ‘*The alterations of THC on sleep EEG and its rebound effect, its side effects before sleep induction, and its residual effects after awakening have contraindicated its clinical use as a sedative hypnotic*’. Data from the clinical research on *Sativex* reviewed in this article are not consistent with this conclusion. Rather, the available evidence to date would suggest that *Sativex* improvement in subjective sleep parameters, and satisfaction in patients with MS and neuropathic pain, with symptomatic relief of pain, spasms, nocturia, and related complaints. From limited sleep-laboratory information, it seems unlikely that its use will result in significant change in sleep architecture. *Sativex* does not benefit all patients, but in those who do respond, the beneficial effects are maintained consistently over time without evidence of tolerance, and are not accompanied by unusual cognitive sequelae [54]. Of course, additional in-depth studies are needed to confirm these contentions and might include formal neuropsychological testing and polysomnography.

Sativex patients and their caregivers have remarked to their physicians how the medicine had transformed their lives through its ability to allow them more restful sleep, increase their daytime level of function, and markedly improve their quality of life. Its addition to the pharmacopoeia may be welcomed by patients, families, and physicians.

REFERENCES

- [1] ‘Brain Basics: Understanding Sleep’, National Institute of Neurological Disorders and Stroke, Bethesda, 2006.
- [2] G. K. Zammit, J. Weiner, N. Damato, G. P. Sillup, C. A. McMillan, *Sleep* **1999**, *22*, S379.
- [3] M. B. Balter, E. H. Uhlenhuth, *J. Clin. Psychiat.* **1992**, *53 Suppl.*, 34; discussion 40–42.
- [4] R. M. Benca, *J. Clin. Psychiat.* **2001**, *62 Suppl. 10*, 33.
- [5] W. Z. Lu, K. A. Gwee, K. Y. Ho, *Eur. J. Gastroenterol. Hepatol.* **2006**, *18*, 623.
- [6] A. I. Pack, D. F. Dinges, P. R. Gehrman, B. Staley, F. M. Pack, G. Maislin, *Ann. Neurol.* **2006**, *59*, 893.
- [7] P. O. Katz, J. M. Scheiman, A. N. Barkun, *Aliment. Pharmacol. Ther.* **2006**, *23 Suppl. 2*, 9.
- [8] D. A. Johnson, *Rev. Gastroenterol. Disord.* **2005**, *5 Suppl. 2*, S3.
- [9] K. P. Parker, D. L. Bliwise, S. Jain, J. Dalton, C. Vena, *J. Clin. Oncol., 2005 ASCO Annual Meeting Proceedings* **2005**, *23*, 8020.
- [10] K. P. Parker, D. L. Bliwise, J. Dalton, W. Harris, S. Jain, M. Kohles-Baker, M. Ribeiro, C. Vena, B. Viswanathan, *J. Clin. Oncol., 2005 ASCO Annual Meeting Proceedings* **2006**, *24*, 8526.
- [11] R. Mechoulam, in ‘The Pharmacohistory of Cannabis sativa’, Ed. R. Mechoulam, CRC Press, Boca Raton, 1986, p. 1–19.
- [12] J. D. Richardson, L. Aanonsen, K. M. Hargreaves, *Eur. J. Pharmacol.* **1997**, *319*, R3.
- [13] J. D. Richardson, L. Aanonsen, K. M. Hargreaves, *J. Neurosci.* **1998**, *18*, 451.
- [14] J. D. Richardson, L. Aanonsen, K. M. Hargreaves, *Eur. J. Pharmacol.* **1998**, *345*, 145.
- [15] J. D. Richardson, S. Kilo, K. M. Hargreaves, *Pain* **1998**, *75*, 111.
- [16] R. G. Pertwee, *Prog. Neurobiol.* **2001**, *63*, 569.
- [17] J. M. Walker, S. M. Huang, N. M. Strangman, K. Tsou, M. C. Sanudo-Pena, *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 12198.
- [18] A. G. Hohmann, R. L. Suplita, N. M. Bolton, M. H. Neely, D. Fegley, R. Mangieri, J. F. Krey, J. M. Walker, P. V. Holmes, J. D. Crystal, A. Duranti, A. Tontini, M. Mor, G. Tarzia, D. Piomelli, *Nature* **2005**, *435*, 1108.
- [19] R. G. Pertwee, in ‘The pharmacology and therapeutic potential of cannabidiol’, Ed. V. DiMarzo, Kluwer Academic, Dordrecht, 2004, p. 32–83.

- [20] R. G. Pertwee, in 'Cannabidiol as a potential medicine', Ed. R. Mechoulam, Birkhäuser, Basel, 2005, p. 47–65.
- [21] A. J. Hampson, M. Grimaldi, J. Axelrod, D. Wink, *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 8268.
- [22] E. B. Russo, G. W. Guy, *Med. Hypotheses* **2006**, *66*, 234.
- [23] A. M. Malfait, R. Gallily, P. F. Sumariwalla, A. S. Malik, E. Andreakos, R. Mechoulam, M. Feldmann, *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 9561.
- [24] E. J. Carrier, J. A. Auchampach, C. J. Hillard, *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 7895.
- [25] J. M. McPartland, E. B. Russo, *J. Cannabis Ther.* **2001**, *1*, 103.
- [26] E. B. Russo, *J. Cannabis Ther.* **2001**, *1*, 21.
- [27] E. Russo, *J. Cannabis Ther.* **2002**, *2*, 5.
- [28] R. G. Pertwee, *Gut* **2001**, *48*, 859.
- [29] E. B. Russo, *Neuroendocrinol. Lett.* **2004**, *25*, 31.
- [30] E. B. Russo, in 'Cannabis in India: Ancient lore and modern medicine', Ed. R. Mechoulam, Birkhäuser, Basel, 2005, p. 1–22.
- [31] C. A. Linné, 'Materia medica per regna tria naturae', Wolfgang Waltherum, Lipsiae et Erlangae, 1772.
- [32] W. B. O'Shaughnessy, *Trans. Med. Phys. Soc. Bengal* **1838–1840**, 71; W. B. O'Shaughnessy, *Trans. Med. Phys. Soc. Bengal* **1838–1840**, 421.
- [33] Y. Gaoni, R. Mechoulam, *J. Am. Chem. Soc.* **1964**, *86*, 1646.
- [34] R. T. Pivik, V. Zarcone, W. C. Dement, L. E. Hollister, *Clin. Pharmacol. Ther.* **1972**, *13*, 426.
- [35] K. Cousins, A. DiMascio, *Psychopharmacologia* **1973**, *33*, 355.
- [36] G. W. Neff, C. B. O'Brien, K. R. Reddy, N. V. Bergasa, A. Regev, E. Molina, R. Amaro, M. J. Rodriguez, V. Chase, L. Jeffers, E. Schiff, *Am. J. Gastroenterol.* **2002**, *97*, 2117.
- [37] S. Walther, R. Mahlberg, U. Eichmann, D. Kunz, *Psychopharmacology (Berlin)* **2006**, *185*, 524.
- [38] E. A. Carlini, J. M. Cunha, *J. Clin. Pharmacol.* **1981**, *21*, 417S.
- [39] V. Santucci, J. J. Storme, P. Soubrie, G. Le Fur, *Life Sci.* **1996**, *58*, PL103.
- [40] R. Mechoulam, E. Fride, L. Hanuš, T. Sheskin, T. Bisogno, V. Di Marzo, M. Bayewitch, Z. Vogel, *Nature* **1997**, *389*, 25.
- [41] T. Kimura, T. Ohta, K. Watanabe, H. Yoshimura, I. Yamamoto, *Biol. Pharm. Bull.* **1998**, *21*, 224.
- [42] E. B. Russo, A. Burnett, B. Hall, K. K. Parker, *Neurochem. Res.* **2005**, *30*, 1037.
- [43] E. B. Russo, C. M. Macarah, C. L. Todd, R. Medora, K. Parker, '41st Annual Meeting of the American Society of Pharmacognosy', Seattle, WA, 2000.
- [44] E. B. Russo, 'Handbook of psychotropic herbs: A scientific analysis of herbal remedies for psychiatric conditions', Haworth Press, Binghamton, 2001.
- [45] G. Buchbauer, L. Jirovetz, W. Jager, C. Plank, H. Dietrich, *J. Pharm. Sci.* **1993**, *82*, 660.
- [46] T. Bisogno, L. Hanuš, L. De Petrocellis, S. Tchilibon, D. E. Ponde, I. Brandi, A. S. Moriello, J. B. Davis, R. Mechoulam, V. Di Marzo, *Br. J. Pharmacol.* **2001**, *134*, 845.
- [47] D. W. Carley, S. Paviovic, M. Janelidze, M. Radulovacki, *Sleep* **2002**, *25*, 391.
- [48] E. Murillo-Rodriguez, D. Millan-Aldaco, M. Palomero-Rivero, R. Mechoulam, R. Drucker-Colin, *FEBS Lett.* **2006**, *580*, 4337.
- [49] E. P. de Meijer, M. Bagatta, A. Carboni, P. Crucitti, V. M. Moliterni, P. Ranalli, G. Mandolino, *Genetics* **2003**, *163*, 335.
- [50] E. de Meijer, in 'The breeding of cannabis cultivars for pharmaceutical end uses', Eds. G. W. Guy, B. A. Whittle, P. Robson, Pharmaceutical Press, London, 2004, p. 55–70.
- [51] E. B. Russo, *J. Cannabis Ther.* **2003**, *3*, 1.
- [52] B. A. Whittle, G. W. Guy, in 'Development of cannabis-based medicines; risk, benefit and serendipity', Eds. G. W. Guy, B. A. Whittle, P. Robson, Pharmaceutical Press, London, 2004, p. 427–466.
- [53] G. W. Guy, P. Robson, *J. Cannabis Ther.* **2003**, *3*, 121.
- [54] E. B. Russo, in 'The Solution to the Medicinal Cannabis Problem', Ed. M. E. Schatman, Taylor & Francis, Boca Raton, 2006, p. 165–194.
- [55] S. Wright, in 'GWMS001 and GWMS0106: maintenance of blinding', GW Pharmaceuticals, London, 2005, p. 8.

- [56] M. P. Barnes, *Expert Opin. Pharmacother.* **2006**, *7*, 607.
- [57] J. Pérez, *Drugs Today* **2006**, *42*, 495.
- [58] A. N. Nicholson, C. Turner, B. M. Stone, P. J. Robson, *J. Clin. Psychopharmacol.* **2004**, *24*, 305.
- [59] J. T. Farrar, J. P. Young Jr., L. LaMoreaux, J. L. Werth, R. M. Poole, *Pain* **2001**, *94*, 149.
- [60] D. T. Wade, P. Makela, P. Robson, H. House, C. Bateman, *Mult. Scler.* **2004**, *10*, 434.
- [61] D. J. Rog, T. Nurmiko, T. Friede, C. Young, *Neurology* **2005**, *65*, 812.
- [62] D. I. Abrams, C. A. Jay, S. B. Shade, H. Vizoso, H. Reda, S. Press, M. E. Kelly, M. C. Rowbotham, K. L. Petersen, *Neurology* **2007**, *68*, 515.
- [63] J. Zajicek, P. Fox, H. Sanders, D. Wright, J. Vickery, A. Nunn, A. Thompson, *Lancet* **2003**, *362*, 1517.
- [64] G. Ernst, C. Denke, M. Reif, M. Schnelle, H. Hagmeister, 'International Association for Cannabis as Medicine', 3rd Conference on Cannabinoids in Medicine, Leiden, The Netherlands, September 9–10, 2005.
- [65] A. Holdcroft, M. Maze, C. Dore, S. Tebbs, S. Thompson, *Anesthesiology* **2006**, *104*, 1040.
- [66] D. T. Wade, P. Robson, H. House, P. Makela, J. Aram, *Clin. Rehabil.* **2003**, *17*, 18.
- [67] W. Notcutt, M. Price, R. Miller, S. Newport, C. Phillips, S. Simmonds, C. Sansom, *Anaesthesia* **2004**, *59*, 440.
- [68] J. S. Berman, C. Symonds, R. Birch, *Pain* **2004**, *112*, 299.
- [69] T. J. Nurmikko, M. G. Serpell, B. Hoggart, P. J. Toomey, B. J. Morlion, '57th Annual Meeting of the American Academy of Neurology', Miami Beach, FL, April 9–16, 2005.
- [70] D. Blake, P. Robson, M. G. Ho, R. W. Jubbs, C. McCabe, *Rheumatology* **2006**, *45*, 50.
- [71] J. R. Johnson, R. Potts, 'The 38th British Pain Society Annual Scientific Meeting', Edinburgh, Scotland, 2005.
- [72] W. G. Notcutt, M. Sharief, I. Mutiboko, C. Hawkes, J. Bolt, N. Sarantis, *Eur. J. Pain* **2007**, in press.
- [73] T. J. Nurmikko, M. G. Serpell, B. Hoggart, P. J. Toomey, B. J. Morlion, *Neurology* **2005**, *64*, A374.
- [74] D. T. Wade, P. M. Makela, H. House, C. Bateman, P. J. Robson, *Mult. Scler.* **2006**, *12*, 639.
- [75] A. J. Budney, J. R. Hughes, B. A. Moore, R. Vandrey, *Am. J. Psychiat.* **2004**, *161*, 1967.
- [76] C. M. Brady, R. DasGupta, C. Dalton, O. J. Wiseman, K. J. Berkley, C. J. Fowler, *Mult. Scler.* **2004**, *10*, 425.
- [77] J. P. Zajicek, H. P. Sanders, D. E. Wright, P. J. Vickery, W. M. Ingram, S. M. Reilly, A. J. Nunn, L. J. Teare, P. J. Fox, A. J. Thompson, *J. Neurol. Neurosurg. Psychiat.* **2005**, *76*, 1664.
- [78] 'Guidance for industry: Botanical drug products', U.S. Department of Health and Human Services, Food and Drug Administration, 2004, p. 48.
- [79] D. P. Tashkin, *Monaldi Arch. Chest Dis.* **2005**, *63*, 93.
- [80] M. E. Lynch, J. Young, 'Symposium on the Cannabinoids', Clearwater, FL, 2005, p. 42.
- [81] A. F. C. Janse, N. S. Breekveldt-Postma, J. A. Erkens, R. M. C. Herings, in Medicinal gebruik van cannabis', PHARMO Instituut (Institute for Drug Outcomes Research), 2004, p. 51.
- [82] R. W. Gorter, M. Butorac, E. P. Cobian, W. van der Sluis, *Neurology* **2005**, *64*, 917.
- [83] N. Figved, G. Klevan, K. M. Myhr, S. Glad, H. Nyland, J. P. Larsen, E. Harboe, R. Omdal, D. Aarsland, *Acta Psychiat. Scand.* **2005**, *112*, 463.
- [84] N. Tachibana, R. S. Howard, N. P. Hirsch, D. H. Miller, I. F. Moseley, D. Fish, *Eur. Neurol.* **1994**, *34*, 320.
- [85] B. R. Stanton, F. Barnes, E. Silber, *Mult. Scler.* **2006**, *12*, 481.
- [86] M. D. Sullivan, J. P. Robinson, *Phys. Med. Rehabil. Clin. N. Am.* **2006**, *17*, 381, vi-vii.
- [87] R. D. Hays, S. A. Martin, A. M. Sesti, K. L. Spritzer, *Sleep Med.* **2005**, *6*, 41.
- [88] T. Tolle, X. Xu, A. B. Sadosky, *J. Diabetes Complications* **2006**, *20*, 26.
- [89] N. Pace, H. C. Frick, K. Sutin, W. Manger, G. Hyman, G. Nahas, in 'The medical use of marihuana and THC in perspective', Eds. G. G. Nahas, K. M. Sutin, D. J. Harvey, S. Agurell, Humana Press, Totowa, 1999, p. 767–780.

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Survey of Australians using cannabis for medical purposes

Wendy Swift*, Peter Gates and Paul Dillon

Address: National Drug and Alcohol Research Centre, University of New South Wales, Sydney, NSW, 2052 Australia

Email: Wendy Swift* - w.swift@unsw.edu.au; Peter Gates - p.gates@unsw.edu.au; Paul Dillon - p.dillon@unsw.edu.au

* Corresponding author

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Abstract

Background: The New South Wales State Government recently proposed a trial of the medical use of cannabis. Australians who currently use cannabis medicinally do so illegally and without assurances of quality control. Given the dearth of local information on this issue, this study explored the experiences of medical cannabis users.

Methods: Australian adults who had used cannabis for medical purposes were recruited using media stories. A total of 147 respondents were screened by phone and anonymous questionnaires were mailed, to be returned by postage paid envelope.

Results: Data were available for 128 participants. Long term and regular medical cannabis use was frequently reported for multiple medical conditions including chronic pain (57%), depression (56%), arthritis (35%), persistent nausea (27%) and weight loss (26%). Cannabis was perceived to provide "great relief" overall (86%), and substantial relief of specific symptoms such as pain, nausea and insomnia. It was also typically perceived as superior to other medications in terms of undesirable effects, and the extent of relief provided. However, nearly one half (41%) experienced conditions or symptoms that were not helped by its use. The most prevalent concerns related to its illegality. Participants reported strong support for their use from clinicians and family. There was almost universal interest (89%) in participating in a clinical trial of medical cannabis, and strong support (79%) for investigating alternative delivery methods.

Conclusion: Australian medical cannabis users are risking legal ramifications, but consistent with users elsewhere, claim moderate to substantial benefits from its use in the management of their medical condition. In addition to strong public support, medical cannabis users show strong interest in clinical cannabis research, including the investigation of alternative delivery methods.

Background

While cannabis has long been part of folk pharmacopeia, there is a burgeoning body of research on its therapeutic potential. This has largely drawn on scientific advances in our understanding of the pharmacology of cannabis, and its complex interactions with the central nervous system, particularly endogenous brain reward pathways [1]. In addition to basic experimental research, case reports, sur-

veys of people using cannabis for medical conditions and prospective clinical trials of cannabis-based medicines are consolidating the evidence that cannabis may play a role in the management of some medical conditions. Authoritative reviews of this evidence indicate that cannabis has therapeutic potential for conditions such as HIV- and cancer-related wasting, nausea and vomiting resulting from

chemotherapy, neurological disorders such as multiple sclerosis and chronic pain [1-4].

While current research reveals exciting therapeutic opportunities, there is an ongoing debate about the virtues of obtaining such benefits from the complex chemical cocktail contained in the whole plant or from one or more components isolated and developed into a synthetic pharmaceutical product. This debate cross-cuts important issues such as the difficulties of reliable dosing when using the natural product, whether the potential harms of smoking cannabis due to its ease of titration overshadow its therapeutic benefits, and whether different medical conditions will respond more favourably to the whole plant or to different constituents in isolation or combination. However, underlying these issues is the reality that most people who use cannabis medicinally do so by using black market supplies of an illicit drug.

As with the opiates, evaluations of the therapeutic potential of cannabis occur in the context of a vigorous political debate on the use of an illicit drug with dependence potential for medicinal purposes. This situation is clearly evident in the United States, where there is an ongoing legal challenge by the Federal Government over the States' rights to allow cannabis to be used by registered medical users. Despite Canada's recent decision to provide a controlled supply of natural cannabis to registered users, and approvals for the marketing of Sativex, a pharmaceutical cannabis extract, in some countries, currently most users would rely on home-grown cannabis, or supplies obtained from friends, families, dealers and medical compassion clubs.

To date, there has been little interest in Australia in formally investigating the therapeutic potential of cannabis or investigating the practices of current medical users. In 1999 the NSW State Government commissioned a Working Party to investigate the issue and recommend research and legislative options. Among their recommendations were: controlled clinical trials of cannabis, investigations into delivery methods other than smoking, surveys of current medical cannabis users and legislative amendments to allow compassionate use [4]. Subsequently, in 2003 the NSW Government announced it would conduct clinical trials, but despite generating significant publicity, there has been no further commitment by the NSW Government on this issue. The 2004 National Drug Strategy Household Survey found widespread public support for medical cannabis use, with 68% supporting a change in legislation to permit use for medical purposes and 74% supporting a clinical trial of medicinal cannabis use [5]. It is not known how many people use cannabis for medicinal purposes in Australia. Those who do use it engage in an illegal behaviour and risk arrest. Those that rely on

black market supplies use a product of unknown source and quality.

Several surveys in the US, UK, Germany and Canada [6-12] have reported perceived improvements in a variety of medical conditions following cannabis use. However, we know very little about the experiences of Australian users, and how they compare to findings in other studies. These authors are aware of only two unpublished Australian studies conducted in northern NSW; in 1998 a survey of 202 users recruited at the Nimbin HEMP Embassy [13], and in 2003 a survey of 48 members of a medical cannabis information service [14].

This paper presents the results of a study of 128 users, which aimed to learn more about their patterns of use, experiences and concerns, and interest in participating in a medical cannabis trial.

Methods

Sample

The sample comprised 128 people who used cannabis for medical purposes. To be eligible for the study, participants had to be living in Australia and to be currently using/have previously used cannabis for medical purposes. While the study targeted residents of Australia's most populous state, NSW (pop: approximately 6.7 million), we did not exclude participants from other parts of Australia (total pop: approximately 20 million).

As it is not known how many Australians use cannabis for medical purposes it was not possible to obtain a representative sample of such users. As this was an exploratory study to see who responded to a general call for participation in the survey, we did not target groups representing people with specific medical conditions (e.g., HIV/AIDS, multiple sclerosis) or hospital departments known to treat patients who may benefit (e.g., oncology, chronic pain clinics). Participants were primarily recruited from opportunistic media stories between November 2003 and August 2004, in newspapers, on radio and television. In addition, the Medical Cannabis Information Service (MCIS) in Nimbin, NSW, offered to tell its members about the survey and the International Association for Cannabis as Medicine (IACM), in Germany, placed the questionnaire on its website.

A total of 147 enquiries were received between December 2003 and August 2004 by telephone and email and approximately 170 questionnaires distributed (some people requested multiple copies to distribute). For example, the media stories generated enquiries from several GPs who said they would inform certain patients of the study. Of the 131 questionnaires returned, 128 were used for analysis (75% of questionnaires sent out). Of the three

Table 1: Conditions/symptoms experienced, duration, and conditions/symptoms requiring cannabis relief (n = 128).

Condition	(%) with condition	Median duration (yrs)	% used cannabis for relief of..*
Depression	60	10	56
Chronic pain	53	10	57
Arthritis	38	9	35
Migraine	22	18	17
Weight loss	21	4	26
Persistent nausea	20	6	27
Spinal cord injury	14	11	13
Spasms (spasticity)	13	8	16
Fibromyalgia	13	13	13
Wasting	13	5	11
ME (chronic fatigue)	13	16	13
Neuralgia/neuropathy	12	8	12
HIV/AIDS	9	15	8
Multiple sclerosis	7	9	7
Cancer	6	10	4
Other neurological disorder	6	5	6
PTSD	5	13	1 person
Irritable bowel syndrome	4	10	1 person
Glaucoma	3	29	2

*These figures do not necessarily equate with the % reporting a particular condition because some people reported using cannabis to relieve the particular symptoms (e.g., chronic pain, nausea) associated with a condition, rather than citing they used cannabis to relieve the condition itself (e.g., arthritis, cancer).

discarded questionnaires, one respondent was a recreational cannabis user and two had never used cannabis.

Questionnaire

The survey comprised an anonymous mail-out questionnaire, adapted from one developed by the MCIS in a recent study of its members [14]. Several issues were covered, including medical conditions/symptoms experienced, patterns of medical cannabis use, symptom relief and effects of use, comparison of cannabis to other medications, source and legal concerns (e.g., arrest), other concerns over use, opinion of family, friends and medical personnel, and interest in participating in a cannabis trial. The final version incorporated comments from researchers and clinicians interested in this issue.

Procedure

The study received ethics approval from the University of New South Wales Social/Health Human Research Ethics Advisory (HREA) Panel. Interested persons were screened for eligibility over the phone and informed of the purpose of the survey; assurances of anonymity and confidentiality were provided. Questionnaires were mailed to participants, completed anonymously and returned in a stamped, self-addressed envelope. Addresses were destroyed when the questionnaire was posted.

Analyses

Data were entered into SPSS (Version 12.0.1). As this was an exploratory study with a small sample size, this paper reports descriptive statistics only. Percentages are presented for categorical data; means (for normally distributed) and medians (for skewed data) are presented for continuous data. While data are usually presented on the overall sample, gender and age differences are presented for some variables, where they are of interest.

Results

Demographics

The sample was 63% male. Participants had a median age of 45 yrs (range 24–88), with almost one third (31%) aged 50 years or over, and one in ten (9%) aged 60 years plus. While the study targeted NSW residents (who represented 58% of participants), responses came from across Australia, especially Queensland (15%) and Victoria (12%). Residents of other States and Territories each comprised less than 3% of participants.

Participants reported a wide range of medical conditions and symptoms associated in the literature with the use of medicinal cannabis (Table 1), most commonly chronic pain (53%) and arthritis (38%). Approximately one in five reported migraine (22%), weight loss (21%) and persistent nausea (20%). However, depression was the most commonly reported condition/symptom (60%). Up to 35 other conditions/symptoms were listed, most commonly

Table 2: Patterns of medical cannabis use (n = 128 unless specified)

	Total (%)	Male (%)	Female (%)
Current use	85	86	83
Length of use			
<1 year	12	9	17
1–5 yrs	27	23	35
6–10 yrs	20	26	10
11–15 yrs	9	10	8
16–20 yrs	10	10	10
>20 yrs	21	23	19
Frequency of use (n = 126)			
several times a day	39	45	29
6–7 days/wk	24	19	31
1–5 days/wk	14	14	13
less than weekly	2	3	2
very seldom	2	1	2
as required	20	18	23
Method(s) of use (n = 127)			
eaten as cooked recipe	49	48	50
drunk as tea	7	8	6
smoked as cigarette (joint)	65	58	77
smoked as dry pipe (chillum)	24	28	19
smoked as water pipe (bong)	54	58	46
vaporiser	8	11	2
eaten as leaf/flower matter	3	4	2
Most helpful method of use (n = 126)			
eaten as cooked recipe	16	15	17
drunk as tea	2	3	2
smoked as cigarette (joint)	31	26	40
smoked as dry pipe (chillum)	10	13	4
smoked as water pipe (bong)	33	36	29
vaporiser	2	3	2
other	6	5	6

post traumatic stress disorder (PTSD) (5%) and irritable bowel syndrome (4%). It is important to note that we did not ask participants to distinguish between primary symptoms/conditions for which they sought treatment (e.g., cancer) and conditions which may have been secondary to this (e.g., depression) or consequent to treatment (e.g., chronic nausea). Multiple conditions (mean = 3.7, SD = 2.1, range = 1–10), of lengthy duration, were the norm, with three quarters (84%) reporting more than one condition and two thirds (67%) at least three conditions. Congruent with this picture, cannabis was used to relieve multiple symptoms (median = 3, range = 1–12), especially chronic pain (57%), depression (56%), arthritis (35%), persistent nausea (27%) and weight loss (26%).

Patterns of medical cannabis use

Participants had first tried cannabis for medical purposes at a median age of 31 years (range = 14–77). More than one quarter (29%) had discovered its therapeutic benefits as a spin-off from recreational use; others had tried it following concerns about the side-effects of their medications (14%), or a belief their medications or treatment were ineffective (13%), or had acted on the recommendation of a medical practitioner (10%) or friend (10%).

Table 2 presents data on patterns of medical use. Most (85%) were currently using cannabis therapeutically, even if sporadically. For those who had stopped, the main reasons were: their inability to obtain a regular supply (9/19 people), its illegality (7/19), cost (7/19) and disliking the side effects or route of use (each 3/19). Of those using intermittently, many reported their use would be more regular if it were more readily availability and cheaper.

Medical use was typically long-term and regular. Use of less than one year was uncommon (12%), with more than half (61%) having used it for at least six years; one in five reported very long-term use (more than 20 years). Most used at least weekly (75%), and more than half (59%) used almost daily or daily. Approximately one in five (22%) specified they used it "as required" for their condition (e.g., when pain was severe). Women tended to report shorter term use than men (52% vs. 31% citing use of 5 years or less).

It was most common for participants' medical use to be stable (22%) or largely unchanged since they started (17%), although it was most common for the amount used to vary according to their condition (35%). About one in ten indicated some increase in dose had been required (12%), while few reported a decrease (5%). Women tended to report more variable (44% vs. 29% of men) or short term use (15% vs. 6% of men); men tended to report an increase in the amount needed (17% vs. 4% of women).

In addition to medical use, three quarters (80%) of participants had used cannabis recreationally. Recreational use was less common among older participants (75% and 97% of recreational users were aged less than 50 years and 65 years, respectively). For almost half (46%), use in the past year had been solely medicinal, but the remainder reported recent recreational use – 29% in the past week, 19% in the past month and a further 6% in the past year.

Route of use

While most people had tried multiple routes for relief, overall smoking was the route most commonly reported (91%). Approximately half the sample (49%) also

smoked tobacco, and two thirds (64.1%) mixed their cannabis with tobacco.

Eating cannabis in cooked recipes was also very prevalent (49%). While vaporisers are not readily available in Australia, 8% had used them. In addition, four people had used tinctures and one used it topically in the bath or as a cream for a skin condition. Overall, smoking was also considered to be the most *helpful* route of use for symptom relief (74%), although concerns about this route of use were widespread. Consistent with Australian research on preferred route of use and age [15], older users (aged 50 years +) typically found joints the most helpful method of use (41% vs. 26% of younger users), while younger users preferred the use of waterpipes (43% vs. 13% of older users).

When asked to comment on the good and bad points of different methods of ingestion the most consistent response was that smoking of any form, particularly with tobacco, was detrimental to respiratory function (and health). This was of particular concern to non-smokers, some of whom did not know how to cook cannabis recipes. Despite attracting the bulk of negative comments, its popularity seemed to lie with its instant effect, its ease of titration and cost-effectiveness compared to the oral route. It seemed to "do the job". Eating was seen to be a much healthier option – it was "safer", tasty when cooked in a recipe, less obvious than smoking and could be done virtually anywhere. Some people liked its slow onset and long-lasting effects, but others claimed difficulties with titration and slow onset made it expensive and ineffective for rapid symptom relief.

Effects of cannabis use

When asked to rate the overall effects of cannabis on a Likert scale ranging from "I feel a lot worse" to "gives me great relief", cannabis was perceived to provide "great relief" (86%) or a little relief (14%). No one believed it had been detrimental to their condition or symptoms.

Positive ratings were ("great" or "good" relief) were also typical for its ability to relieve specific symptoms (Table 3). In addition, several other symptoms were noted, primarily insomnia (13% used for insomnia; of these 82% derived "great" relief).

Approximately three quarters of participants (71%) claimed to have experienced a return of their symptoms or condition on stopping cannabis, especially: pain (53% of those who claimed a return of symptoms), depression or anxiety (30%), insomnia (11%), spasm (10%) and nausea/vomiting or lack of appetite (9%).

Table 3: Symptom relief (n = 128)

Symptom relief required...*	Total (%)	Male (%)	Female (%)
Nausea relief	48	56	44
Of these, received:			
great relief	53	51	62
good relief	44	46	35
no effect	3	3	4
Pain relief	83	83	83
Of these, received:			
great relief	55	49	65
good relief	45	52	35
no effect	0	0	0
Ability to cope emotionally	66	70	60
Of these, received:			
great relief	45	40	54
good relief	54	58	46
no effect	1	2	0
Appetite stimulant	51	55	44
Of these, received:			
great relief	52	55	48
good relief	46	46	48
no effect	2	0	5
Decrease in spasms/tremor	39	36	44
Of these, received:			
great relief	43	43	43
good relief	55	54	57
no effect	2	4	0
Relief through relaxation	83	88	75
Of these, received:			
great relief	72	69	78
good relief	28	31	22
no effect	0	0	0

* No-one reported their condition was made worse

Only one in ten (11%) participants reported symptoms they believed were unrelated to their medical condition upon stopping cannabis, citing symptoms congruent with cannabis withdrawal such as anxiety or mood disturbance (including paranoia), insomnia, loss of appetite, restlessness and vivid dreams.

Comparison with other medicines

Almost two thirds (62%) of respondents claimed that they decreased or discontinued their use of other medicines when they started using cannabis medicinally. This was more common in males (65% vs. 58% of females) and older participants (aged 50 years +) (70% vs. 59% among younger participants). For some people this was a

Table 4: Comparison of cannabis with other medications (n = 128 unless specified).

	Total	Male	Female
Decreased or discontinued use of other medicines (n = 117*)	62%	65	58
Comparison of undesirable effects (n = 125)			
Cannabis produced much worse effects than other medicines	1	0	2
Cannabis produced somewhat worse effects	2	4	0
Undesired effects about the same	8	8	9
Other meds produced somewhat worse effects than cannabis	16	14	19
Other medicines produced much worse effects than cannabis	41	40	43
I have no undesirable effects from cannabis	31	33	28
Other medicines work differently	1	1	0
Comparison of relief provided (n = 118*)			
Other medicines work much better than cannabis	3	0	7
Other medicines work a bit better than cannabis	3	4	0
Other medicines work about the same as cannabis	9	8	9
Cannabis works a bit better than other medicines	13	11	15
Cannabis works much better than others medication	54	58	48
Only cannabis gives me relief from my condition	15	15	15
Other medicines work differently	2	0	4
Can't distinguish – use them together	1	1	2
Use cannabis to relieve side effects of other medicines	1	1	0

*Some people did not use other medications concurrently

substantial change, representing a shift away from chronic, high-dose medication use.

Perhaps not surprisingly, cannabis was typically perceived as superior to other medications in terms of undesirable effects, and the extent of relief provided (Table 4). Thus, cannabis was rated to produce equivalent (8%) or worse side effects (3%) by a minority of therapeutic users. It was considered to work "a bit" or "much better" than other medicines, or to be the only source of relief, by more than three quarters (82%). Two participants made the interesting comment that cannabis worked *differently* to other medicines, so could not be directly compared.

Despite the very positive response to the use of cannabis, nearly one half (41%; 36% of men and 50% of women) found it did not help certain conditions/symptoms. Almost one third (29%) said cannabis was less effective for certain types of pain, or extreme pain, with a further 12% specifying migraine or headache pain. Nearly one in ten (8%) reported no effect on depression or anxiety. More than one in ten (14%) specified that while cannabis could ease their symptoms and enabled them to cope, they realised that it could not cure their underlying condition. Younger participants were more likely than older participants to claim a condition not helped by cannabis (45% vs. 32% of those aged 50 years +).

Supply issues

Participants obtained medical cannabis from multiple sources (median = 1, range = 1–6; 44% had two or more sources), especially friends or family (58%) and dealers (42%). A substantial proportion grew their own (38%) while few (6%) obtained it from a compassion club or cooperative. Among those who purchased cannabis, the median weekly outlay was \$50 (range = \$1–\$500, n = 95).

When asked to comment on the variability of the cannabis they used, those who could obtain a consistent supply of high quality cannabis that suited their needs were in the minority. Typically, participants noticed variability along a number of lines, such as potency, effectiveness, intoxication and side-effects, which made titration difficult. While some noted the importance of factors such as the part of the plant used (e.g., leaf versus head/buds), strain (e.g., *sativa* versus *indica*), soil and climate, the overwhelming responses focussed on hydroponic versus soil-grown cannabis ("bush bud" or home grown cannabis), and home grown cannabis versus purchased cannabis.

Hydroponic cannabis was almost universally unpopular and was avoided where possible – despite its greater potency, it was also considered shorter acting, produced greater tolerance and worse side-effects than other cannabis. By comparison, soil-grown cannabis was perceived to

be less unpleasantly potent, natural ("organic"), less chemically treated, and with fewer side-effects. However, it was also perceived as harder to get. Home grown cannabis was seen as the best method of obtaining a consistent, safe supply of medicinal quality. A common response was that purchased cannabis was not to be trusted, and that unscrupulous growers who were more concerned with yield and greed compromised the quality of their crop with chemicals such as growth hormone and pesticides.

Concerns

A minority (13%) had no concerns over their medical cannabis use. Concerns over potential health effects (32%) or the risk of dependence (21%) were overshadowed by those relating to its illegal status (76%), the fear of being arrested (60%) and cost (51%). Indeed, one quarter (27%) claimed to have been arrested, cautioned or convicted in relation to their medical cannabis use, with this outcome more commonly reported by men (31% vs. 19% of women) and younger users (30% vs. 16% of users aged 50 years +). Other concerns mentioned (15%) were: the stigma of using, issues around parenting, pregnancy and relationships, availability, quality and difficulties in dose adjustment.

Support from others and interest in clinical trial

Most participants had a regular doctor (90%) and about a half had a regular specialist (55%). Virtually all (90%) had informed a clinician of their therapeutic use, typically reporting a supportive response from GPs (75% of those told), specialists (74%) and nurses (81%). Family and friends were largely considered supportive of the participant's use (71%).

Not surprisingly, there was widespread support for Government provision of cannabis to patients in a variety of circumstances. At least three quarters supported the supply of cannabis to any patient who was permitted to use it by being registered under a Government scheme (82%); more specifically, those patients who: could not afford to buy it on a regular basis (82%), could only purchase it on the black market (81%), couldn't ensure a consistent supply (75%), or were worried about quality control issues (77%). More than half endorsed the supply of patients who did not know anyone capable of growing it (72%), were concerned about hydroponically grown cannabis (72%), or who needed a supply quickly (66%).

Although not all participants were NSW residents, there was almost universal interest (89%) in participating in a clinical trial, in which a controlled supply of cannabis was grown and provided to registered medical cannabis users. There was also strong, although lesser, interest in trying alternative delivery methods such as a spray or tablet (79%).

While for some people, the availability of any cannabis-derived product that worked was their prime concern, alternative delivery methods were considered attractive as they obviated the necessity to smoke, removed concern about engaging in illegal behaviour and having to access the black market, and were more portable and acceptable than smoking. The main caveats on an alternative were that it was easy to titrate, quick, efficient, reliable and natural or safe – sprays and vaporisers were mentioned specifically by some as preferable to pills in this regard. A clear theme was the desire to keep the holistic, natural properties of cannabis rather than produce a chemical/synthetic drug with numerous binding and carrying agents. Nevertheless, there was recognition that different medical conditions may require different approaches, such as different active agents (e.g., THC versus other cannabinoids), strains or methods (e.g., slow release pill versus fast-acting spray).

The main reason for not supporting alternatives appeared to be that using the whole plant in its natural state was perceived to be the best method. In addition, for some the ritual of cannabis use was perceived as part of its medicinal benefit. There was also concern at political interference and its potential for exploitation and corruption in a trial.

Discussion

This exploratory study examined the patterns of medicinal cannabis use among a sample of 128 Australian adults who responded to media stories about this issue. Firstly, we need to acknowledge its limitations. As we do not know how many Australians use cannabis medicinally or their characteristics, we relied on the recruitment of volunteers through purposive sampling. Instead of targeting a particular group we used media stories disseminated widely on the radio, television and in newspapers to attract a cross-section of people. Thus, these results may not be representative of the experiences of all medicinal users, and may be affected by selection bias by excluding those who did not have access to these media, who did not wish to or could not contact us or did not return the questionnaire. We also attracted participants whose experiences with medical cannabis were typically positive, so they have little to tell us about people who have not found cannabis helpful or pleasant therapeutically. However, they still provide important information on these people's experiences, and raise important issues regarding the use of black market supplies of the cannabis plant and the development of cannabis-based pharmaceuticals. As the questionnaire was self-completed, there was potential for misunderstanding of the questions. However, the wording was straightforward, contact details were provided in the event of misunderstanding, and the results were remarkably consistent across participants, which encour-

ages us that the questions were understood. Despite being anonymous, several participants provided us with contact details in case further information was needed, and wrote additional comments about their experiences and attitudes. In addition, many of the findings are remarkably consistent with the findings of other local and international studies, as indicated below.

People in this study reported regular, ongoing medical use over quite long periods – with 61% using for more than five years and 20% reporting very long-term use of more than 20 years. However, as Ware and colleagues noted in their study of almost 1000 medical users [10], this was a group of chronically ill people with multiple long-standing conditions. The perceived need for alternative or additional symptom relief may reflect the fact that we recruited a sample of particularly entrenched medicinal cannabis users who were dissatisfied with conventional treatments, that medicinal cannabis use is more likely to be considered an option by people who find conventional treatments and medications unsatisfactory, or that many had been exposed to its perceived medical benefits quite early due to their recreational use. Larger studies addressing a broad cross-section of users may better answer this question.

Consistent with the literature on the conditions for which cannabis has been indicated, chronic pain, arthritis, persistent nausea and weight loss were among the most common conditions for which cannabis relief was sought. However, depression was the most common condition: more than half (56%) used cannabis to relieve depression, and two thirds (66%) used it to cope emotionally, universally obtaining great or good relief. Other studies have also reported cannabis use for the relief of depression, although not at this level [8-10,14]. The relationship between depression and cannabis use is controversial, with recent literature indicating that cannabis use may be implicated in depression and suicidal thoughts and behaviours. This would suggest that regular medicinal use may be contraindicated by placing people at risk of depression or self-harm. However, we do not know the type or aetiology of the depression cited by our participants. Many may have experienced depression and stress associated with their physical condition, which may have been alleviated along with any physical relief. The risk may also be greatest among heavy, younger users and those who may already be vulnerable to mental ill health due to their life circumstances [16-18]. Medical cannabis use patterns may not typically be regular enough to pose a great risk. Regardless, it is important that people considering the use of medical cannabis are aware of the risks of use [19]. A recent paper [20] has suggested that THC and cannabidiol, two major components of cannabis, may help alleviate bipolar disorder, recommending a pharmaceutical

product would be a safer option than crude cannabis, in which the balance of components is variable.

Consistent with local and international research on people with a variety of medical conditions [8-12,14], most participants claimed moderate to substantial benefits from cannabis, both in terms of their overall condition and management of individual symptoms. It was typically considered more effective and less aversive than other medications in managing their condition(s), the symptoms of which commonly re-emerged upon stopping (71%). While their use was often complementary to other medications and treatment, 62% had decreased or discontinued use of other medications when they commenced medicinal cannabis use. Nevertheless, cannabis was not a panacea – it did not help all conditions, particularly certain types of pain, and there was recognition that while it substantially improved quality of life it was not a cure. This is not necessarily surprising, as overall well-being and specific symptoms have multiple causes and can be affected by several factors, and is borne out by recent controlled clinical trials, for example, on chronic pain [21].

As others have reported (e.g., [8-10]) we also found that in addition to medical use, recreational use was common: most (80%) had used cannabis recreationally, with about one half (54%) of these reporting some recent use. Indeed, 29% had discovered its therapeutic potential through their recreational use. One participant raised the issue that part of the therapeutic effect for them was the ritual of use and the "high" experienced [6]. This demonstrates the difficulty of precisely identifying the therapeutic component when people are using the natural plant matter, and will continue to present a challenge for the development of cannabis pharmaceuticals. While some people may find the illegality, route of use and psychoactive effects of natural cannabis undesirable and prefer a manufactured pharmaceutical product, several in this survey claimed to prefer the holistic delivery of all the compounds present when using the natural plant. We need to know more about the effect of the different active chemicals on medical conditions and how their therapeutic potential is mediated by the context of use.

Nonetheless, this was not simply a sample of recreational users, especially as we attracted many older users who used exclusively for medical reasons (75% of those aged 50 years+). They did not fit the recreational user stereotype, were willing to take the risk of using an illicit drug, exposure to the illicit drug market and the possibility of arrest to gain symptom relief. Indeed, the most common concern over medicinal use was its illegality, fear of arrest and cost (all >50%). One quarter (27%) of participants had experienced legal ramifications due to their use. Several people commented that they had no alternative than

using an illegal drug, claiming that other medicines with negative and toxic effects (e.g., opiates) were legally prescribed, and that if nothing else worked for them they had the right to access cannabis without fear or stigma. Several made pleas for medical cannabis use to be treated as a medical, rather than a legal, issue, as their health and quality of life were at stake.

Smoking was the most common method of use; in addition, many were tobacco smokers or mixed cannabis with tobacco. Given the similarities between cannabis and tobacco smoke this is of particular concern for people who are ill, especially those with compromised immune systems. Despite acknowledgement of the risks of smoking and concerns expressed over its effects, it was considered the most helpful route of use. While eating was perceived as much healthier, until satisfactory solutions are achieved on titration and dosing issues, smoking will no doubt continue to be a popular method of obtaining relief.

Cannabis dependence was a concern for one in five participants (21%). This study provided indirect evidence that participants were unlikely to experience withdrawal symptoms on ceasing medical use, but this was only a crude measure. While the risk of dependence is probably low when used medicinally, this risk needs to be weighed up with the other concerns of the patient – for example, it may be low on the list of concerns for those with terminal illness [19].

Finally, participants reported that family and friends were likely to know about and support their medical cannabis use. These data also indicate that the medical profession is encountering, and frequently supporting, patients who use cannabis for symptom relief. Given their central role in the management of illness, it is important that clinicians are educated about the effects of cannabis, in order to assist patients in making informed decisions about their treatment. There was also clearly great interest among participants in a clinical trial and scope to investigate methods of delivery that avoid the health concerns associated with smoking cannabis, keeping in mind that some participants were reluctant to use a pharmaceutical product. In addition to distrust of unscrupulous participants in the black market, some were also distrustful of Government's motives and role in therapeutic research. It is therefore vital that any clinical trials are conducted in a rigorous, independent manner.

Conclusion

Overall, these findings are consistent with those of other surveys, in revealing the perceived effectiveness of cannabis for the relief of symptoms associated with several medical conditions. While a small study, it has several

implications. Firstly, people are risking the use of an illicit drug for its perceived therapeutic effects, and in some cases being arrested. Secondly, they are informing their clinicians about their medical use and frequently receiving support, highlighting the importance of ensuring clinicians are informed about cannabis. Finally, in addition to strong public support, medical cannabis users show strong interest in clinical cannabis research, including the investigation of alternative delivery methods.

Competing interests

The author(s) declare they have no competing interests.

Authors' contributions

WS conceived the study, designed the methodology, adapted the questionnaire, cleaned and analysed the data and wrote the paper.

PG assisted in questionnaire adaptation, managed data collection, entered the data, assisted with preliminary data analyses and commented on the manuscript.

PD assisted in questionnaire adaptation, recruited participants and commented on the manuscript.

All authors read and approved the final manuscript.

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References

1. Grotenhermen F, Russo E: **Cannabis and cannabinoids: Pharmacology, toxicology and therapeutic potential.** NY, Haworth Integrative Healing Press; 2002.
2. Joy JE, Watson SJ, Benson JA: **Marijuana and medicine: Assessing the science base.** Washington, DC, National Academy Press; 1999.
3. House of Lords Select Committee on Science and Technology: **Cannabis: The scientific and medical evidence.** London, The Stationery Office; 1998.
4. New South Wales Parliament. Working Party on the Use of cannabis for Medical Purposes: **Report of the Working Party on the use of cannabis for medical purposes.** Sydney, New South Wales Parliament. Working Party on the Use of cannabis for Medical Purposes; 2000:42.
5. Australian Institute of Health and Welfare: **2004 National Drug Strategy Household Survey: First results.** Canberra, Australian Institute of Health and Welfare; 2005.
6. Coomber R, Oliver M, Morris C: **Using cannabis therapeutically in the UK: A qualitative analysis.** *Journal of Drug Issues* 2003, **33**:325.
7. Gieringer D: **Medical use of cannabis: Experience in California.** In *Cannabis and cannabinoids: Pharmacology, toxicology and therapeutic potential* Edited by: Grotenhermen F and Russo E. NY, Haworth Integrative Press; 2002:143-151.
8. Grotenhermen F, Schnelle M: **Survey on the medical use of cannabis and THC in Germany.** *Journal of Cannabis Therapeutics* 2003, **3**:17-40.
9. Ogborne AC, Smart RG, Weber T, Birchmore-Timney C: **Who is using cannabis as a medicine and why: An exploratory study.** *Journal of Psychoactive Drugs* 2000, **32**:435-443.

10. Ware MA, Adams H, Guy GW: **The medicinal use of cannabis in the UK: results of a nationwide survey.** *International Journal of Clinical Practice* 2005, **59**:291-295.
11. Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ: **Cannabis use for chronic non-cancer pain: results of a prospective study.** *Pain* 2003, **102**:211-216.
12. Ware MA, Rueda S, Singer J, Kilby D: **Cannabis use by persons living with HIV/AIDS: patterns and prevalence of use.** *Journal of Cannabis Therapeutics* 2003, **3**:3-15.
13. Helliwell D: **Medicinal Cannabis survey.** [<http://www.medicineau.net.au/clinical/drug&alcohol/drug&alcohol290.html>].
14. Kavalas A: **Medical uses of cannabis: Information for medical practitioners.** Sydney, Inn Press; 2004.
15. Hall W, Swift W: **The THC content of cannabis in Australia: Evidence and implications.** *Australian and New Zealand Journal of Public Health* 2000, **24**:503-508.
16. Rey JM, Sawyer MG, Raphael B, Patton GC, Lynskey M: **Mental health of teenagers who use cannabis: results of an Australian survey.** *British Journal of Psychiatry* 2002, **180**:216-221.
17. Fergusson DM, Horwood LJ, Swain-Campbell NR: **Cannabis dependence and psychotic symptoms in young people.** *Psychological Medicine* 2003, **33**:15-21.
18. Patton GC, Coffey C, Carlin JB, Degenhardt L, Lynskey M, Hall W: **Cannabis use and mental health in young people: cohort study.** *British Medical Journal* 2002, **325**:1195-1198.
19. Swift W, Hall W: **Cannabis and dependence.** In *Cannabis and cannabinoids: Pharmacology, toxicology, and therapeutic potential* Edited by: Grotenhermen F and Russo E. NY, Haworth Integrative Healing Press; 2002.
20. Ashton CH, Moore PB, Gallagher P, Young AH: **Cannabinoids in bipolar affective disorder: a review and discussion of their therapeutic potential.** *Journal of Psychopharmacology* 2005, **19**:293-300.
21. Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, Sansom S: **Initial experiences with medicinal extracts of cannabis for chronic pain: Results from 34 "N of 1" studies.** *Anaesthesia* 2004, **59**:440-452.

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Therapeutic Benefits of Cannabis: A Patient Survey

Charles W. Webb MD and Sandra M. Webb RN, BSN

Abstract

Clinical research regarding the therapeutic benefits of cannabis ("marijuana") has been almost non-existent in the United States since cannabis was given Schedule I status in the Controlled Substances Act of 1970. In order to discover the benefits and adverse effects perceived by medical cannabis patients, especially with regards to chronic pain, we hand-delivered surveys to one hundred consecutive patients who were returning for yearly re-certification for medical cannabis use in Hawai'i.

The response rate was 94%. Mean and median ages were 49.3 and 51 years respectively. Ninety-seven per cent of respondents used cannabis primarily for chronic pain. Average pain improvement on a 0-10 pain scale was 5.0 (from 7.8 to 2.8), which translates to a 64% relative decrease in average pain. Half of all respondents also noted relief from stress/anxiety, and nearly half (45%) reported relief from insomnia. Most patients (71%) reported no adverse effects, while 6% reported a cough or throat irritation and 5% feared arrest even though medical cannabis is legal in Hawai'i. No serious adverse effects were reported.

These results suggest that Cannabis is an extremely safe and effective medication for many chronic pain patients. Cannabis appears to alleviate pain, insomnia, and may be helpful in relieving anxiety. Cannabis has shown extreme promise in the treatment of numerous medical problems and deserves to be released from the current Schedule I federal prohibition against research and prescription.

Introduction

Research into the therapeutic benefits of cannabis has been severely limited by the federal Schedule I classification, which essentially prohibits any ability to acquire or to provide cannabis for studies investigating possible therapeutic effects. Limited studies have been done in Canada and in Europe, as well as several in California.

Hawai'i is one of twenty states (plus the District of Columbia) which allow certifications for use of medical cannabis. The authors have been certifying patients for use of medical cannabis in Hawai'i for more than four years. In an attempt to discover the perceived benefits and adverse effects of medical cannabis, we conducted a survey of medical cannabis patients.

Methods

Sample Selection

Between July of 2010 and February of 2011, we hand-delivered questionnaires to one hundred consecutive patients who had been certified for the medical use of cannabis for a minimum of one year and were currently re-applying for certification.

Survey Design and Administration

The subjects were verbally instructed to complete the questionnaire in the office at the time of re-certification or were provided a stamped and addressed envelope so they could complete the questionnaire at home. All patients were instructed to remain anonymous and to answer the questions as honestly as possible.

A universal pain scale was used to assess pain before and after treatment (0 = no pain, 10 = worst pain ever). Open-ended questions were asked to ascertain the following:

- (1) "Any adverse effects you have had from using medical cannabis?"
- (2) "Does medical cannabis help you with any other problems? If so, what?"

The purpose of the last question was to explore benefits outside the parameters of the state of Hawai'i's medical cannabis qualifying conditions.

Results

The overall response rate was 94%. The mean age was 49.3 years and the median age was 51. No data was collected on sex or race/ethnicity. Almost all respondents (97%) used medical cannabis primarily for relief of chronic pain.

Average reported pain relief from medical cannabis was substantial. Average pre-treatment pain on a zero to ten scale was 7.8, whereas average post-treatment pain was 2.8, giving a reported average improvement of 5 points. This translates to a 64% average relative decrease in pain.

Other reported therapeutic benefits included relief from stress/anxiety (50% of respondents), relief of insomnia (45%), improved appetite (12%), decreased nausea (10%), increased focus/concentration (9%), and relief from depression (7%). Several patients wrote notes (see below) relating that cannabis helped them to decrease or discontinue medications for pain, anxiety, and insomnia. Other reported benefits did not extend to 5% or more of respondents.

Six patients (6%) wrote brief notes relating how cannabis helped them to decrease or to discontinue other medications. Comments included the following: "Medical cannabis replaced my need for oxycodone. Now I don't need them at all." "I do not need Xanax anymore." "In the last two years I have been able to drop meds for anxiety, sleep, and depression." "I've cut back 18 pills on my morphine dosage."

A majority (71%) reported no adverse effects, while 6% reported a cough and/or throat irritation and 5% reported a fear of arrest. All other adverse effects were less than 5%. No serious adverse effects were reported.

Discussion

According to the Institute of Medicine, chronic pain afflicts 116 million Americans and costs the nation over \$600 billion every year in medical treatment and lost productivity.¹ Chronic pain is a devastating disease that frequently leads to major depression and even suicide.² Unfortunately, the therapeutic options for chronic pain are limited and extremely risky.

Spurred by efforts to encourage physicians to become more pro-active in treating chronic pain, US prescription opioids (synthetic derivatives of opium) have increased ten-fold since 1990.³ By 2009 prescription opioids were responsible for almost half a million emergency department visits per year.⁴ In 2010 prescription opioid overdoses were responsible for well over 16,000 deaths.⁵ A 2010 article in the *New England Journal of Medicine* addressing this problem is aptly titled “A Flood of Opioids, a Rising Tide of Deaths.”³ Drugs such as OxyContin[®] are so dangerous that the manufacturer’s boxed warning states that “respiratory depression, including fatal cases, may occur with use of OxyContin, even when the drug has been used as recommended and not misused or abused.”⁶ Clearly safer analgesics are needed.

The Hippocratic Oath reminds to “first, do no harm.” It cannot be over-emphasized that there has never been a death from overdose attributed to cannabis.⁷ In fact, no deaths whatsoever have been attributed to the direct effects of cannabis.⁷ Cannabis has a safety record that is vastly superior to all other pain medications.

Many physicians worry that cannabis smoke might be as dangerous as cigarette smoke; however, epidemiologic studies have found no increase in oropharyngeal or pulmonary malignancies attributable to marijuana.⁸⁻¹⁰ Still, since smoke is something best avoided, medical cannabis patients are encouraged to use smokeless vaporizers which can be purchased on-line or at local “smoke-shops.” In states that (unlike Hawai‘i) allow cannabis dispensaries, patients can purchase “vapor pens,” analogous to e-cigarettes and fully labeled regarding doses of THC and other relevant cannabinoids.

Tests have proven that smoke-free vaporizers deliver THC as well or even more efficiently than smoking, and that most patients prefer vaporizers over smoking.¹¹ Like smoking, vaporizers allow patients to slowly titrate their medicine just to effect, analogous to IV patient-controlled analgesia (PCA) that has been so successful in hospital-based pain control. This avoids the unwanted psychoactive side-effects often associated with oral medication such as prescription Marinol[®] (100% THC in oil) capsules which tend to be slowly and erratically absorbed and are often either ineffectually weak or overpoweringly strong.^{12,13} Because inhaled cannabis is rapid, reliable, and titratable, most patients strongly prefer inhaled cannabis over Marinol[®] capsules.¹⁴

While the relative safety of cannabis as medication is easily established, the degree of efficacy is still being established. The reported pain relief by patients in this survey is enormous. One reason for this is that patients were already self-selected for success: they had already tried cannabis and found that it worked for them. For this sample, the benefits of cannabis outweighed any negative effects. The study design may therefore lend itself to over-estimating the benefits and under-estimating the negative side-effects if extrapolated to the general population.

Another reason that the reported pain relief is so significant is that cannabis has been proven effective for many forms of

recalcitrant chronic pain. A University of Toronto systematic review of randomized controlled trials (RCT’s) examining cannabinoids in the treatment of chronic pain found that fifteen of eighteen trials demonstrated significant analgesic effect of cannabinoids and that there were no serious adverse effects.¹⁵

While opioids are generally considered to have little benefit in chronic neuropathic pain, several RCT’s have shown that cannabinoids can relieve general neuropathic pain,¹⁶ as well as neuropathic pain associated with HIV and with multiple sclerosis (MS).^{17,18} One study found that cannabis had continuing efficacy at the same dose for at least two years.¹⁹

Even low dose inhaled cannabis has been proven to reduce neuropathic pain. In a randomized, double-blind, placebo-controlled crossover trial involving patients with refractory neuropathic pain, Ware, et al, found that therapeutic blood levels of THC (mean 45 ng/ml achieved by a single inhalation three times a day) were much lower than those necessary to produce a cannabis euphoria or “high”(> 100 ng/ml).¹⁹

Cannabis is relatively non-addicting, and patients who stop using it (eg, while traveling) report no withdrawal symptoms. One author (Webb C.) worked for 26 years in a high volume emergency department where he never witnessed a single visit for cannabis withdrawal symptoms, whereas dramatic symptoms from alcohol, benzodiazepine, and/or opioid withdrawal were a daily occurrence.

So why is cannabis still held hostage by the DEA as a Schedule I substance? On June 18, 2010, the Hawai‘i Medical Association passed a resolution stating in part that:

“Whereas, 1) Cannabis has little or no known withdrawal syndrome and is therefore considered to be minimally or non-addicting; and

Whereas, 2) Cannabis has many well-known medical benefits (including efficacy for anorexia, nausea, vomiting, pain, muscle spasms, and glaucoma) and is currently recommended by thousands of physicians; and

Whereas 3) Cannabis has been used by millions of people for many centuries with no history of recorded fatalities and with no lethal dosage ever discovered; and

Whereas, Cannabis therefore fulfills none of the required three criteria (all of which are required) to maintain its current restriction as a Schedule I substance...

The Hawai‘i Medical Association recommends that Medical Cannabis be re-scheduled to a status that is either equal to or less restrictive than the Schedule III status of synthetic THC (Marinol[®]), so as to reduce barriers to needed research and to humanely increase availability of cannabinoid medications to patients who may benefit.”²⁰

Medical cannabis remains controversial mainly because the federal government refuses to recognize cannabis as an accepted medication. To this we would echo the words of Melanie Thernstrom in her excellent book *The Pain Chronicles*,² “How could treating pain be controversial?” one might ask, “ Why wouldn’t it be treated? Who are the opponents of relief?”

Conclusions

Cannabis is an extremely safe and effective medication for many patients with chronic pain. In stark contrast to opioids and other available pain medications, cannabis is relatively non-addicting and has the best safety record of any known pain medication (no deaths attributed to overdose or direct effects of medication). Adverse reactions are mild and can be avoided by titration of dosage using smokeless vaporizers.

More research needs to be pursued to discover degrees of efficacy in other areas of promise such as in treating anxiety, depression, bipolar disorder, autism, nausea, vomiting, muscle spasms, seizures, and many neurologic disorders. Patients deserve to have cannabis released from its current federal prohibition so that scientific research can proceed and so that physicians can prescribe cannabis with the same freedom accorded any other safe and effective medications.

Conflict of Interest

None of the authors identify a conflict of interest.

Authors' Biography:

Dr. Webb graduated from Dartmouth Medical School (BS Medicine) and from UC San Francisco School of Medicine (MD 1974). General Residency US Public Health Hospital (San Francisco) and Highland Hospital (Oakland). Emergency Medicine Physician 1975-2006 (Colorado), Urgent Care Physician 2007-present (Kailua Kona). Sandra Webb RN, since 1979 (emergency and radiology nurse). Dr. Webb and nurse Webb have been certifying patients for medical use of cannabis since 2009.

Authors' Affiliation:

- Keauhou Urgent Care Center, 78-6831 Alii Dr., Suite 418, Kailua Kona, HI 96740

Correspondence to:

Charles W. Webb MD; 73-993 Ahikawa St, Kailua Kona, HI 96740;
Email: forecharlee@msn.com

References

1. Institute of Medicine of the National Academy. *Relieving Pain in America*. 2011.
2. Themstrom M. *The Pain Chronicles*. New York: Farrar, Straus and Giroux; 2011.
3. Oakie S. A Flood of Opioids, a Rising Tide of Death. *NEJM*. 2010;363:1981-1985.
4. Substance Abuse and Mental Health Services Admin. Drug Abuse Warning Network: selected tables of national estimates of drug-related emergency visits. Rockville, MD: Center for Behavioral Health Statistics and Quality, SAMHSA; 2010.
5. CDC. *Opioids Drive Continued Increase in Drug Overdose Deaths*. Press release Feb 20, 2013.
6. Purdue Pharma LP. *An Overview of the Oxycontin Label Update Deterrence Studies*. 07/13.
7. Iverson LL. *The Science of Marijuana*. New York: Oxford University Press; 2000.
8. Sidney S, Beck JE, Tekawa IS, Quesenberry CP, Friedman GC. Marijuana use and mortality. *Am J Public Health*. 1997; 87(4):585-590.
9. Hashibe M, Straif K, Tashkin DP, Morgenstern H, Greenland S, Zhang ZF. Epidemiologic review of marijuana use and cancer risk. *Alcohol*. 2005;35(3):265-275.
10. Tashkin DP. Smoked marijuana as a cause of lung injury. *Monaldi Arch Chest Dis*. 2005;63(2):93-100.
11. Abrams D, et al. Vaporization as a Smokeless Cannabis Delivery System. *Clin. Pharmacol. Ther*. 2007;82(5):572-578.
12. Institute of Medicine. *Marijuana and Medicine: Assessing the Science Base*. 1999.
13. Weil A. *San Francisco Chronicle*. June 6, 2002.
14. Grinspoon L. "I have yet to examine a patient who has used both smoked marijuana and Marinol who finds the latter more useful." *International Journal of Drug Policy*. 2001 Issue.
15. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systemic review of randomized trials. *Br. J. Clin Pharmacol*. 2011 Nov; 72(5):735-44.
16. Wilsey B, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain*. 2008;9(6):506-521.
17. Abrams D, et al. Cannabis in Painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology*. 2007; 68(7):515-521.
18. Rog, et al. Oromucosal THC/cannabidiol for neuropathic pain associated with MS. *Clin Ther*. 2007;29(9):2068-2079.
19. Ware MA, Ducruet T, Robinson AR. Evaluation of herbal cannabis characteristics by medical users: a randomized trial. *Harm Reduction J*. 2006 Nov 13;3:32.
20. Hawaii Medical Association Resolution, June 18, 2010.



CLINICAL REVIEW

Effect of illicit recreational drugs upon sleep: Cocaine, ecstasy and marijuana

Thomas Schierenbeck^a, Dieter Riemann^a,
Mathias Berger^a, Magdolna Hornyak^{a,b,*}

^a Department of Psychiatry and Psychotherapy, Freiburg University Medical Center, Hauptstrasse 5, D-79104 Freiburg, Germany

^b Interdisciplinary Pain Center, Freiburg University Medical Center, Hauptstrasse 5, D-79104 Freiburg, Germany

KEYWORDS

Cocaine;
Ecstasy;
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Marijuana;
Tetrahydrocannabinol;
Recreational drugs;
Sleep;
Withdrawal

Summary The illicit recreational drugs cocaine, ecstasy and marijuana have pronounced effects upon sleep. Administration of cocaine increases wakefulness and suppresses REM sleep. Acute cocaine withdrawal is often associated with sleep disturbances and unpleasant dreams. Studies have revealed that polysomnographically assessed sleep parameters deteriorate even further during sustained abstinence, although patients report that sleep quality remains unchanged or improves. This deterioration of objective sleep measures is associated with a worsening in sleep-related cognitive performance. Like cocaine, 3,4-methylenedioxymethamphetamine (MDMA; "ecstasy") is a substance with arousing properties. Heavy MDMA consumption is often associated with persistent sleep disturbances. Polysomnography (PSG) studies have demonstrated altered sleep architecture in abstinent heavy MDMA users. Smoked marijuana and oral Δ -9-tetrahydrocannabinol (THC) reduce REM sleep. Moreover, acute administration of cannabis appears to facilitate falling asleep and to increase Stage 4 sleep. Difficulty sleeping and strange dreams are among the most consistently reported symptoms of acute and subacute cannabis withdrawal. Longer sleep onset latency, reduced slow wave sleep and a REM rebound can be observed. Prospective studies are needed in order to verify whether sleep disturbances during cocaine and cannabis withdrawal predict treatment outcome.

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Abbreviations: CBD, cannabidiol; d, days; MDE, 3,4-methylenedioxy-N-ethylamphetamine; MDMA, 3,4-methylenedioxymethamphetamine; MSLT, multiple sleep latency test; PSG, polysomnography; pts, patients; SE, sleep efficiency; SOL, sleep onset latency; SWS, slow wave sleep; THC, Δ -9-tetrahydrocannabinol; TST, total sleep time; WASO, wakefulness after sleep onset.

* Corresponding author at: Department of Psychiatry and Psychotherapy and Interdisciplinary Pain Center, Freiburg University Medical Center, Hauptstrasse 5, D-79104 Freiburg, Germany. Tel.: +49 761 270 5118; fax: +49 761 270 5013.

Introduction

“Recreational drug use” is a term for a substance use pattern that has become highly prevalent. Recreational drug users are generally well-integrated and may belong to any social class. They usually resort to illegal drugs at weekend parties, in order to reduce stress and to escape from the daily routine. Also, the substances are welcome for their socializing properties, and some of them for their enhancement of dancing capabilities.

This review considers the illicit recreational drugs cocaine, ecstasy and marijuana. Further examples of substances used in the described manner are amphetamine, methamphetamine, LSD, psilocybin mushrooms, ketamine and gamma-hydroxybutyrate. Many of these drugs, in particular cocaine, are clearly not restricted to a recreational pattern of use.

It is estimated that 42% of US American adolescents have experience with marijuana before the end of secondary school, 9% with cocaine and 7% with ecstasy.¹ An estimated 4.2 million Americans are classified with current dependence on or abuse of marijuana, and almost 1.7 million with dependence on or abuse of cocaine.² These numbers are higher than the corresponding figures for prescription-type pain relievers used nonmedically (1.6 million), prescription-type tranquilizers (400,000) and heroin (300,000).²

We carried out a search in the electronic databases Medline (since 1966), Embase, PsycINFO, Psynex and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). The key words included “cocaine”, “3,4-methylenedioxymethamphetamine”, “MDMA” and “ecstasy” as well as “cannabis”, “marijuana”, “tetrahydrocannabinol” and “THC”. These terms were entered into the databases in conjunction with the term “sleep”. Articles published until August 2007 were eligible, and reference lists of relevant articles were screened for further related studies.

Cocaine

Acute cocaine administration

The competitive inhibition of presynaptic dopamine transporters in the nucleus accumbens and prefrontal cortex, leading to an increase in dopamine availability, has been proposed to constitute the primary neurophysiologic equivalent of central cocaine effects.³ Acute subjective effects of cocaine intake are euphoria, orgiastic feelings, restlessness, motor activation and increased alertness.

Trouble sleeping is a frequently cited adverse effect of cocaine intake.^{4,5} Polysomnography (PSG) studies have confirmed the stimulant properties of cocaine, demonstrating longer sleep latency, reduced total sleep time and suppression of REM sleep after acute cocaine administration.^{6–8} Acute effects of cocaine upon sleep resemble those of other psychostimulants such as amphetamine.⁹

Cocaine withdrawal

During acute withdrawal, cocaine-dependent individuals often experience depressed mood, psychomotor agitation or retardation, increased appetite, fatigue, sleep disturbances and unpleasant dreams.^{10,11}

To date, eight PSG studies^{7,8,12–17} of cocaine withdrawal have been published, mostly non-randomized controlled trials (see Table 1). Three studies administered cocaine in simulated binges during the inpatient phase.^{8,16,17} Results were similar to the studies with previous binges in the patients’ natural environment.^{12–15} It has been shown that during acute cocaine withdrawal, total sleep time is significantly reduced,^{8,12–17} approximating that of untreated chronic insomniacs.²¹ Sleep onset latency is prolonged and sleep efficiency is decreased.^{8,12–18} An increase in REM sleep percentage and reduced REM latency are observed.^{7,8,12–16} These changes in REM sleep are consistent with the subjective withdrawal symptom of increased dreaming.^{10,11} It has been found that smaller doses of cocaine administered in the morning may improve sleep in cocaine-dependent subjects, probably by attenuating withdrawal effects.¹⁹

During the subacute phase of cocaine withdrawal, commonly defined as starting on day 10, PSG parameters of sleep continuity deteriorate even further. Total sleep time decreases,^{12–14,16,17} and sleep latency and sleep efficiency also change in the direction of even poorer sleep.^{12–14,16,17} REM latency remains significantly reduced.^{12,14,16}

It has been shown that cognitive performance deteriorates during subacute cocaine withdrawal.^{17,20} Reaction time on a vigilance task increases,^{17,20} which is considered to be a sensitive measure of growing sleep pressure in the context of sleep deprivation.²¹ Also, the sleep-dependent performance on a motor sequence task is compromised and correlates with an individual’s total sleep during withdrawal.¹⁷

These findings are most notable in view of the fact that subjective sleep quality remains unchanged or improves during subacute withdrawal.^{12,16,17,22,23} This phenomenon is the exact opposite of the

Table 1 PSG studies investigating sleep during cocaine withdrawal

Authors	Subjects (no.)	Intervention	Method	Major findings
Watson et al. ⁷	3 light cocaine users	1 drug night, 3 d recovery	PSG	Drug night: ↓ REM sleep. Recovery: REM rebound
Kowatch et al. ¹²	3 cocaine-dependent	17 d abstinence	PSG, subjective reports	↑ Wakefulness, ↓ SE, ↓ SWS, REM rebound, subjective: about same as usual
Gillin et al. ¹³	6 stimulant abusers	Placebo arm of lisuride treatment trial, 18 d abstinence	PSG	↑ SOL, ↓ TST, ↓ SWS, REM rebound
Thompson et al. ¹⁴	7 stimulant abusers	14 d abstinence	PSG	Acute withdrawal: REM rebound, subacute withdrawal: ↓ TST
Lukas et al. ¹⁵	20 cocaine- and heroin-dependent	9 d abstinence before buprenorphine treatment	PSG	↑ SOL, ↓ TST, ↓ SE, ↓ SWS, REM rebound
Johanson et al. ⁸	3 cocaine-dependent	8–10 d abstinence, 5 d of 600 mg cocaine, 15–16 d abstinence	PSG, MSLT	Cocaine use: ↑ SOL, ↓ SE, ↓ REM sleep. Withdrawal: ↑ SOL, ↓ SE, ↓ REM latency, MSLT: ↑ SOL during subacute withdrawal
Pace-Schott et al. ¹⁶	5 cocaine-dependent	3 d abstinence, 3 d of 600 mg crack, 15 d abstinence	PSG, subjective reports, cognitive tasks	↑ SOL, ↓ SE, ↓ REM latency across binge-abstinence, subjective: slight improvement, deterioration of cognitive performance
Morgan et al. ¹⁷	12 cocaine-dependent	3 d abstinence, 3 d of 223 mg cocaine, 17 d abstinence	PSG, spectral power, subjective reports, cognitive tasks	↑ SOL, ↓ TST, ↓ SE across binge-abstinence, ↑ δ spectral power during subacute withdrawal, subjective: improvement, deterioration of cognitive performance

Abbreviations: d, days; MSLT, multiple sleep latency test; PSG, polysomnography; SE, sleep efficiency; SOL, sleep onset latency; SWS, slow wave sleep; TST, total sleep time.

distorted sleep perception in primary insomniacs, who typically underestimate their sleep quality. It has not been studied why cocaine-dependent subjects do not recognize this deterioration of sleep during subacute withdrawal. A possible explanation is that, although slow wave sleep (SWS) percentage is low both during acute and subacute withdrawal,^{12–14,17} δ spectral power may increase during subacute withdrawal.¹⁷ An increased δ spectral power is associated with better self-reports of sleep quality.²⁴

Ecstasy

Acute and subacute ecstasy effects

3,4-Methylenedioxymethamphetamine (MDMA; “ecstasy”) is a drug that is frequently used by visitors of raves or techno parties in large dance

clubs. MDMA induces rapid release of serotonin via interaction with presynaptic serotonin uptake carriers.²⁵ MDMA also induces rapid dopamine release and binds to a variety of neurotransmitter receptors, especially serotonin 5-HT₂ receptors.²⁵ MDMA effects such as feelings of closeness to others, increased empathy and self-perception are summarized as the “entactogenic” properties of this agent (“entactogen” from Greek and Latin, “producing a touching within”). Furthermore, ingestion of ecstasy is associated with cognitive and perceptual changes that resemble effects of psychedelics and with amphetamine-like hyperactivity and increased energy.

MDMA users commonly report restless, disturbed sleep during the 48 h following MDMA intake.^{26,27} 3,4-Methylenedioxy-*N*-ethylamphetamine (MDE; “eve”) has similar effects as MDMA. The only PSG investigation on acute effects of entactogens was conducted with MDE. It showed an increase in

wakefulness and an almost complete suppression of REM sleep.²⁸

Persistent effects of heavy ecstasy use

A number of studies have indicated that heavy MDMA use is associated with persistent neuropsychiatric symptoms such as, most notably, impaired episodic memory and learning performance,²⁹ but also anxiety, depersonalization, depression, and sleep disturbances.^{26,30–32} Interpretation of these studies is complicated owing to methodological difficulties such as polydrug usage and the possibility of pre-existing differences.

There is conflicting evidence with respect to the PSG patterns in abstaining heavy MDMA users. A recent study³³ replicated earlier findings³⁴ that Stage 2 sleep is reduced in these individuals. Furthermore, Stage 1 sleep is increased and total sleep time is reduced, although findings were only near-significant in one study and significant in the other. There was a trend for reduced REM latency.³³ No significant correlations were detected between previous marijuana use and Stage 2 or Stage 1 sleep.³³ In a third PSG study of abstinent MDMA users, Stage 2 sleep was decreased without achieving statistical significance.³⁵ Furthermore, this study indicated that sleep efficiency and SWS are increased in ecstasy users.³⁵ However, these latter findings need to be viewed cautiously since control subjects had remarkably low sleep efficiency and decreased SWS.³⁵

Cannabis

Acute and chronic cannabis administration

The cannabis plant contains over 60 cannabinoids. Δ -9-Tetrahydrocannabinol (THC) is the constituent that is mainly responsible for the psychotropic effects of marijuana.³⁶ These psychotropic effects are mediated mostly by cannabinoid CB₁-receptors, which can be found in high concentrations in the frontal cortex, cerebellum and basal ganglia.³⁷ CB₁-receptors activate a variety of signal transduction pathways and interact with numerous neurotransmitters and neuromodulators. Acute subjective marijuana effects are highly variable, and contradictory effects may be observed depending on individual and condition. Often, marijuana induces mild euphoria, talkativeness, intensification of sensory experiences, difficulty concentrating, altered time perception, relaxation and drowsiness.

Interpretation of the available PSG studies of cannabis effects is difficult due to a number of

methodological limitations. Sample sizes were often small, and most studies were carried out in the 1970s. There is considerable heterogeneity with respect to administered dosage, time and route of administration, specificity for THC, and, notably, the extent of previous drug consumption, possibly leading to withdrawal effects during baseline or to tolerance. Several studies have shown that acute administration of THC decreases sleep latency,³⁸ and is associated with reports of greater ease in getting to sleep.^{39,40} Yet, arousing effects may predominate initially, and in a few studies with high THC doses or marijuana-naïve subjects, findings were more suggestive of increments in sleep onset latency.^{41–43} There is some evidence indicating that cannabis reduces Stage 3, but increases Stage 4 and total slow wave sleep,^{45–47} but contradictory effects have also been observed.⁴¹ Furthermore, it has been found consistently that THC decreases total REM sleep and REM density.^{41,46,48–51} Owing to the slow elimination of THC and its active metabolites, sedative effects are sometimes still present the following morning.^{38,47} The combination of THC with cannabidiol, an important non-psychoactive ingredient of marijuana, leads to an increase in wakefulness compared to THC alone.⁴⁷

PSG studies of chronic marijuana administration have suggested that some tolerance occurs to the sleep-inducing^{52,53} and SWS-enhancing^{45,51,52} effects of cannabis. Tolerance to REM sleep effects may be less pronounced,⁴⁶ but evidence is conflicting.^{48,53} A study of subjective changes of marijuana effects over the years indicated that desirable effects of marijuana upon sleep are reported less frequently after years of use compared to initial ratings.⁵⁴

Table 2 gives an overview over studies investigating the effects of cannabis upon objective sleep measures.

Cannabis withdrawal

Anger and irritability, anxiety and nervousness, restlessness, weight loss, sleep difficulty and strange dreams are frequently reported marijuana withdrawal effects.^{55–57} Less common symptoms are depressed mood, chills, shakiness, stomach pain and sweating.⁵⁵ Cannabis withdrawal resembles nicotine withdrawal with respect to symptom profile, magnitude and time course.^{58,59}

There is quite a substantial number of recent studies on subjective sleep measures during cannabis withdrawal.⁵⁵ Difficulty in sleeping and strange dreams have been reported with high cross-study reliability.⁵⁵ They generally occur within 24–72 h of discontinuation of cannabis use

Table 2 Studies investigating the effect of smoked marijuana and oral THC upon sleep

Study	Subjects (no.)	Intervention	Major findings
Gillin et al. ⁴²	3 psychiatric pts	40 mg THC	↓ REM sleep
Kales et al. ⁴⁷	4 naive, 4 chronic users	Smoked marijuana	↓ REM sleep. Recovery: REM rebound
Freemon ⁴⁸	2	20 mg THC	↓ REM %. Recovery: ↑ wakefulness, ↓ REM latency
Pivik et al. ⁶⁵	6	<20 mg THC	↓ WASO. Recovery: ↓ Stage 1, ↓ REM latency
Cousens and DiMascio ³⁸	9 insomniacs	10–30 mg THC	↓ Sleep onset latency
Bobon et al. ⁴³	1 psychiatric pt	20 mg Δ -8-THC	↑ Wakefulness, ↑ REM latency
Hosko et al. ⁴⁴	7 (2 naive, 1 heavy user)	20 mg THC	No consistent alterations
Pranikoff et al. ⁵²	30 chronic users	Smoked marijuana until "high"	↑ Stage 2, ↓ Stage 4 compared to abstinent users
Barratt et al. ⁴⁵	12	2 marijuana cigarettes (1.6% THC)	Acute: ↑ SWS, chronic administration: ↓ SWS. Withdrawal: ↓ SWS
Feinberg et al. ⁴⁶	7 chronic users	70–210 mg THC	↑ Stage 4, ↓ REM density, ↓ REM sleep. Withdrawal: ↑ SOL, ↓ SWS, REM rebound
Tassinari et al. ⁴¹	8 (7 naive)	70 mg THC	↑ Stage 2, ↓ REM sleep
Feinberg et al. ⁵⁰	4 chronic users	Marijuana extract (70–210 mg THC)	Low dosage: ↑ Stage 4, ↓ REM density. Withdrawal: ↑ SOL
Karacan et al. ⁵³	32 chronic users	Usual pattern of marijuana use	↑ REM %, ↑ SOL
Freemon ⁵¹	2	30 mg THC	Chronic administration: ↓ SWS. Withdrawal: ↑ wakefulness, ↓ SWS
Nicholson et al. ⁴⁷	8	15 mg THC, 5 mg THC+CBD, 15 mg THC+CBD	15 mg THC: ↑ sleepiness next morning. 15 mg THC+CBD: ↑ wakefulness, ↓ Stage 3, ↑ sleepiness next morning
Walther et al. ⁸⁹	6 pts with dementia and nighttime agitation	2.5 mg THC	↓ Nocturnal motor activity

Abbreviations: CBD, cannabidiol; MSLT, multiple sleep latency test; PSG, polysomnography; pts, patients; SOL, sleep onset latency; SWS, slow wave sleep; THC: Δ -9-tetrahydrocannabinol; TST, total sleep time; WASO, wakefulness after sleep onset.

and persist for 6–7 weeks.^{57,60} Resumption of cannabis use attenuates sleep disturbances.^{61–63} Treatment of cannabis withdrawal symptoms by means of oral substitution of THC improves sleep or even reinstates subjectively normal sleep.^{40,64}

The available PSG studies of cannabis withdrawal were designed as non-randomized, controlled trials. They have demonstrated increments in sleep onset latency and wakefulness after sleep onset.^{46,49–51} Total SWS is reduced^{45,46,51} and REM sleep is increased^{46,48,49,65}. This increase in REM sleep is consistent with the subjective abstinence symptom of "strange dreams".^{55,56}

Outlook

Every year, a combined 2.2 million Americans receive treatment for cocaine or cannabis abuse in specialized facilities, compared to 2.5 million alcoholics receiving specialized treatment.²

Treatment of cocaine and cannabis dependence is difficult and expensive.^{66,67} More research on potential pharmacotherapies is warranted.

It can be hypothesized that the poor sleep quality during cocaine withdrawal has detrimental effects upon treatment outcome. The demonstrated impairments of vigilance and learning performance may put cocaine users at increased risk of relapse. On the other hand, it has been shown that the severity of withdrawal symptoms including sleep disturbances predicts poor treatment outcome in cocaine dependence.⁶⁸ Similarly, it has been suggested that in cannabis dependence, sleep problems and other withdrawal symptoms make cessation more difficult and that resumption of cannabis use serves as a negative reinforcer.^{57,69,70} There is need for prospective studies to verify whether sleep disturbances during cocaine and cannabis withdrawal are predictive of relapse. Such a relationship would not only provide a prognostic tool, but it might also open new

perspectives on therapeutic strategies. In alcohol addiction, the predictive value of sleep disturbances for relapse has been established,^{71–73} and successful treatment options have been derived from this observation.⁷⁴

Substances recently tested as pharmacotherapy for cocaine abuse interact directly with sleep–wake mechanisms. The effectiveness of substances with gamma amino butyric acid (GABA)-mediated sedative properties such as baclofen has been demonstrated.^{75–77} Modafinil acts in the opposite direction, and constitutes another promising candidate for treatment of cocaine dependence.^{78,79} It is a stimulant substance that may be able to restore cognitive functioning in cocaine withdrawal, as it does in sleep-deprived individuals when given in the morning.⁸⁰ The question of whether modafinil possesses abuse potential is discussed controversially at present.^{81,82} There is need for randomized controlled trials that examine the effect of GABA-medications and stimulants such as modafinil upon objective sleep measures, cognitive performance as well as treatment outcome. This would shed more light upon the clinical relevance of the impairments of sleep-dependent cognitive performance.

Agonist replacement therapy has become a well-established approach to treat opiate and nicotine dependence. Preliminary findings of substitution therapy for cannabis dependence are promising,^{40,64} demonstrating an attenuation of withdrawal symptoms including sleep disturbances. Randomized controlled trials on the effect of THC substitution upon treatment outcome are under way.

The question of whether MDMA induces serotonin neurotoxicity in humans has become a field of extensive research.²⁹ Since PSG is a highly sensitive instrument to detect subtle neurophysiologic alterations, it might prove to be particularly useful in this matter.

Individuals who are exposed to experimental depletion of the serotonin precursor tryptophan develop acute serotonin deficiency. PSG studies of tryptophan depletion have been carried out in healthy individuals^{83–86} and in psychiatric patients.^{85–88} The bottom line of these studies is that tryptophan depletion is associated with an increase in wakefulness and Stage 1 sleep and with a reduction in Stage 2 sleep. Phasic activity of REM sleep is enhanced.

These PSG patterns are in agreement with the sleep architecture observed in abstinent heavy MDMA users.^{33,34} Prospective PSG studies are needed in order to investigate preexisting differences in sleep architecture between consequent

MDMA users and non-user controls. Such prospective studies would also be capable of determining to what extent restitution occurs with prolonged abstinence. To this end, ecstasy users and controls would need to be followed up over a period of several years. Furthermore, it should be determined whether PSG abnormalities correlate with other presumed evidence of MDMA neurotoxicity such as PET examinations using serotonin transporter ligands.²⁹

There is evidence that the sedative properties of marijuana may be of use in clinical practice. An open pilot study demonstrated the effectiveness and tolerability of THC for the treatment of agitated behavior at night in patients with severe dementia.⁸⁹ Nocturnal motor activity was reduced by 59% from baseline, as evidenced by wrist actigraphy. Other parameters such as appetite disturbances and irritability improved as well. No adverse effects were observed after single and repeated administrations of THC. A systematic review found that atypical antipsychotics often fail to reduce behavioral symptoms of dementia.⁹⁰ Adverse effects occur frequently.⁹⁰ For safety concerns, co-administration of benzodiazepines is not recommended.⁹¹ The limitations of the available treatment options warrant the search for effective and well-tolerated alternatives. Randomized controlled trials with large sample sizes and longer treatment periods are needed in order to corroborate the preliminary findings for THC.

Cannabis-based medicines have also been shown to improve subjective sleep quality in patients with chronic pain syndromes, such as multiple sclerosis, peripheral neuropathy, rheumatoid arthritis and cancer pain.⁹² To a great extent, this improvement may be due to analgesic, anti-inflammatory and spasmolytic effects³⁶ resulting in nocturnal symptom relief, in addition to the hypnotic properties of cannabis.

Practice points

1. Consider and routinely investigate the possibility that complaints of sleep disturbances may be related to use of illicit drugs, especially in younger patients.
2. In cocaine- or cannabis-dependent individuals, sleep disturbances including unpleasant dreams constitute important withdrawal symptoms and their treatment needs to be incorporated into the overall treatment plan.

3. Even if subjective assessments suggest normal or only slightly disturbed sleep during subacute cocaine withdrawal, PSG parameters may reveal considerable sleep disturbance. This sleep disturbance contributes to a deterioration of cognitive performance.

Research agenda

1. Prospective studies on the predictive value of sleep disturbances during cocaine and cannabis withdrawal for long-term outcome.
2. Randomized controlled trials of cocaine withdrawal investigating the effect of GABA-medications and stimulant substances (e.g. modafinil) upon objective sleep measures, cognitive performance and treatment outcome.
3. Prospective PSG studies of ecstasy use, in order to investigate preexisting differences in sleep patterns and to detect to what extent restitution occurs with continued abstinence.
4. Randomized controlled trials of THC for treatment of selected types of sleep disturbances such as circadian rhythm disturbances in patients with dementia.

References

1. National Institute on Drug Abuse. *Monitoring the future. National results on adolescent drug use. Overview of key findings 2006* [Online]; 2006 [cited September 10, 2007] [76 screens]. Available from: <<http://www.monitoringthefuture.org/>>.
2. National Survey on Drug Use and Health. *Results from the 2006 National Survey on Drug Use and Health: national findings* [Online]; 2006 [cited September 10, 2007] [282 screens]. Available from: <<http://nsduhweb.rti.org/>>.
3. Vetulani J. Drug addiction. Part II. Neurobiology of addiction. *Pol J Pharmacol* 2001;**53**:303–17.
4. Smith DE, Schwartz RH, Martin DM. Heavy cocaine use by adolescents. *Pediatrics* 1989;**83**(4):539–42.
5. Williamson S, Gossop M, Powis B, et al. Adverse effects of stimulant drugs in a community sample of drug users. *Drug Alcohol Depend* 1997;**44**(2/3):87–94.
6. Post RM, Gillin JC, Wyatt RJ, et al. The effect of orally administered cocaine on sleep of depressed patients. *Psychopharmacologia* 1974;**37**(1):59–66.
7. Watson R, Bakos L, Compton P, et al. Cocaine use and withdrawal: the effect on sleep and mood. *Am J Drug Alcohol Abuse* 1992;**18**(1):21–8.
- *8. Johanson CE, Roehrs T, Schuh K, et al. The effects of cocaine on mood and sleep in cocaine-dependent males. *Exp Clin Psychopharmacol* 1999;**7**(4):338–46.
9. Feinberg I, Hibi S, Cavness C, et al. Sleep amphetamine effects in MBDS and normal subjects. *Arch Gen Psychiatry* 1974;**31**(5):723–31.
10. Brower KJ, Maddahian E, Blow FC, et al. A comparison of self-reported symptoms and DSM-III-R criteria for cocaine withdrawal. *Am J Drug Alcohol Abuse* 1988;**14**(3):347–56.
11. Cottler LB, Shillington AM, Compton WM, et al. Subjective reports of withdrawal among cocaine users: recommendations for DSM-IV. *Drug Alcohol Depend* 1993;**33**:97–104.
12. Kowatch RA, Schnoll SS, Knisely JS, et al. Electroencephalographic sleep and mood during cocaine withdrawal. *J Addict Dis* 1992;**11**(4):21–45.
13. Gillin JC, Pulvirenti L, Withers N, et al. The effects of lisuride on mood and sleep during acute withdrawal in stimulant abusers: a preliminary report. *Biol Psychiatry* 1994;**35**:843–9.
14. Thompson PM, Gillin JC, Golshan S, et al. Polygraphic sleep measures differentiate alcoholics and stimulant abusers during short-term abstinence. *Biol Psychiatry* 1995;**38**(12):831–6.
15. Lukas SE, Dorsey CM, Mello NK, et al. Reversal of sleep disturbances in cocaine- and heroin-dependent men during chronic buprenorphine treatment. *Exp Clin Psychopharmacol* 1996;**4**(4):413–20.
- *16. Pace-Schott EF, Stickgold R, Muzur A, et al. Sleep quality deteriorates over a binge-abstinence cycle in chronic smoked cocaine users. *Psychopharmacology* 2005;**179**(4):873–83.
- *17. Morgan PT, Pace-Schott EF, Sahul ZH, et al. Sleep, sleep-dependent procedural learning and vigilance in chronic cocaine users: evidence for occult insomnia. *Drug Alcohol Depend* 2006;**82**(3):238–49.
18. Jacobs GD, Pace-Schott EF, Stickgold R, et al. Cognitive behavior therapy and pharmacotherapy for insomnia: a randomized controlled trial and direct comparison. *Arch Intern Med* 2004;**164**(17):1888–96.
19. Dudish-Poulsen S, Hatsukami DK. Acute abstinence effects following smoked cocaine administration in humans. *Exp Clin Psychopharmacol* 2000;**8**(4):472–82.
20. Pace-Schott EF, Stickgold R, Muzur A, et al. Cognitive performance by humans during a smoked cocaine binge-abstinence cycle. *Am J Drug Alcohol Abuse* 2005;**31**(4):571–91.
21. Graw P, Kräuchi K, Knoblauch V, et al. Circadian and wake-dependent modulation of fastest and slowest reaction times during the psychomotor vigilance task. *Physiol Behav* 2004;**80**(5):695–701.
22. Gawin FH, Kleber HD. Abstinence symptomatology and psychiatric diagnosis in cocaine abusers. Clinical observations. *Arch Gen Psychiatry* 1986;**43**:107–13.
23. Weddington WW, Brown BS, Haertzen CA, et al. Changes in mood, craving, and sleep during short-term abstinence reported by male cocaine addicts. A controlled, residential study. *Arch Gen Psychiatry* 1990;**47**(9):861–8.
24. Krystal AD, Edinger JD, Wohlgemuth WK, et al. NREM sleep EEG frequency spectral correlates of sleep complaints in primary insomnia subtypes. *Sleep* 2002;**25**(6):630–40.
25. Green AR, Mehan AO, Elliott JM, et al. The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). *Pharmacol Rev* 2003;**55**(3):463–508.
26. Verheyden SL, Henry JA, Curran HV. Acute, sub-acute and long-term subjective consequences of 'ecstasy' (MDMA) consumption in 430 regular users. *Hum Psychopharmacol* 2003;**18**(7):507–17.

* The most important references are denoted by an asterisk.

27. Huxster JK, Pirona A, Morgan MJ. The sub-acute effects of recreational ecstasy (MDMA) use: a controlled study in humans. *J Psychopharmacol* 2006;**20**(2):281–90.
- *28. Gouzoulis E, Steiger A, Ensslin M, et al. Sleep EEG effects of 3,4-methylenedioxyamphetamine (MDA; "eve") in healthy volunteers. *Biol Psychiatry* 1992;**32**(12):1108–17.
29. Gouzoulis-Mayfrank E, Daumann J. Neurotoxicity of methylenedioxyamphetamines (MDMA; ecstasy) in humans: how strong is the evidence for persistent brain damage? *Addiction* 2006;**101**(3):348–61.
30. Cohen RS. Subjective reports on the effects of the MDMA ('ecstasy') experience in humans. *Prog Neuro-psychopharmacol Biol Psychiatry* 1995;**19**(7):1137–45.
31. Parrott AC, Sisk E, Turner JJ. Psychobiological problems in heavy 'ecstasy' (MDMA) polydrug users. *Drug Alcohol Depend* 2000;**60**(1):105–10.
32. Dughiero G, Schifano F, Forza G. Personality dimensions and psychopathological profile of ecstasy users. *Hum Psychopharmacol Clin* 2001;**16**(8):635–9.
- *33. McCann UD, Peterson SC, Ricaurte GA. The effect of catecholamine depletion by alpha-methyl-para-tyrosine on measures of cognitive performance and sleep in abstinent MDMA users. *Neuropsychopharmacology* 2007;**32**:1695–706.
34. Allen RP, McCann UD, Ricaurte GA. Persistent effects of (+/-)3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") on human sleep. *Sleep* 1993;**16**(6):560–4.
35. Ricaurte GA, McCann UD. Experimental studies on 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") and its potential to damage brain serotonin neurons. *Neurotoxicity Res* 2001;**3**(1):85–99.
36. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 2003;**42**(4):327–60.
37. Iversen L. Cannabis and the brain. *Brain* 2003;**126**:1252–70.
38. Cousens K, DiMascio A. (–) Delta 9 THC as an hypnotic. An experimental study of three dose levels. *Psychopharmacologia* 1973;**33**(4):355–64.
39. Chait LD. Subjective and behavioral effects of marijuana the morning after smoking. *Psychopharmacology* 1990;**100**(3):328–33.
40. Haney M, Hart CL, Vosburg SK, et al. Marijuana withdrawal in humans: effects of oral THC or divalproex. *Neuropsychopharmacology* 2004;**29**(1):158–70.
41. Tassinari CA, Ambrosetto G, Peraita-Adrado MR, et al. The neuropsychiatric syndrome of Δ -9-tetrahydrocannabinol and cannabis intoxication in naive subjects: a clinical and polygraphic study during wakefulness and sleep. In: Braude MC, Szara S, editors. *Pharmacology of marijuana*. New York: Raven Press; 1976. p. 357–75.
42. Gillin JC, Kotin J, Post R, et al. Sleep during one week of administration of Δ -9 tetrahydrocannabinol to psychiatric patients. *J Sleep Res* 1972;**1**:44.
43. Bobon DP, Schulz H, Mattke D, et al. Influence of synthetic-8-tetrahydrocannabinol on all-night sleep EEG in man. In: Jovanovic UJ, editor. *The nature of sleep*. Stuttgart: Gustav Fischer Verlag; 1973.
44. Hosko MJ, Kochar MS, Wang RI. Effects of orally administered delta-9-tetrahydrocannabinol in man. *Clin Pharmacol Ther* 1973;**14**(3):344–52.
45. Barratt ES, Beaver W, White R. The effects of marijuana on human sleep patterns. *Biol Psychiatry* 1974;**8**(1):47–54.
- *46. Feinberg I, Jones R, Walker JM, et al. Effects of high dosage delta-9-tetrahydrocannabinol on sleep patterns in man. *Clin Pharmacol Ther* 1975;**17**(4):458–66.
- *47. Nicholson AN, Turner C, Stone BM, et al. Effect of Delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. *J Clin Psychopharmacol* 2004;**24**(3):305–13.
48. Kales A, Hanley J, Rickles W, et al. Effects of marijuana administration and withdrawal in chronic users and naive subjects. *Psychophysiology* 1972;**9**:92.
49. Freemon FR. Effects of marijuana on sleeping states. *JAMA* 1972;**220**(10):1364–5.
50. Feinberg I, Jones R, Walker J, et al. Effects of marijuana extract and tetrahydrocannabinol on electroencephalographic sleep patterns. *Clin Pharmacol Ther* 1976;**19**(6):782–94.
51. Freemon FR. The effect of chronically administered delta-9-tetrahydrocannabinol upon the polygraphically monitored sleep of normal volunteers. *Drug Alcohol Depend* 1982;**10**(4):345–53.
52. Prankoff K, Karacan I, Larson EA, et al. Effects of marijuana smoking on the sleep EEG. Preliminary studies. *J Fla Med Assoc* 1973;**60**(3):28–31.
53. Karacan I, Fernandez-Salas A, Coggins WJ, et al. Sleep electroencephalographic–electrooculographic characteristics of chronic marijuana users: part I. *Ann N Y Acad Sci* 1976;**282**:348–74.
54. Halikas JA, Weller RA, Morse CL, et al. A longitudinal study of marijuana effects. *Int J Addict* 1985;**20**(5):701–11.
- *55. Budney AJ, Hughes JR, Moore BA, et al. Review of the validity and significance of cannabis withdrawal syndrome. *Am J Psychiatry* 2004;**161**(11):1967–77.
56. Vandrey R, Budney AJ, Kamon JL, et al. Cannabis withdrawal in adolescent treatment seekers. *Drug Alcohol Depend* 2005;**78**(2):205–10.
57. Copersino ML, Boyd SJ, Tashkin DP, et al. Cannabis withdrawal among non-treatment-seeking adult cannabis users. *Am J Addict* 2006;**15**(1):8–14.
58. Vandrey RG, Budney AJ, Moore BA, et al. A cross-study comparison of cannabis and tobacco withdrawal. *Am J Addict* 2005;**14**(1):54–63.
59. Vandrey RG, Budney AJ, Hughes JR, et al. A within-subject comparison of withdrawal symptoms during abstinence from cannabis, tobacco, and both substances. *Drug Alcohol Depend*, in press.
60. Budney AJ, Moore BA, Vandrey RG, et al. The time course and significance of cannabis withdrawal. *J Abnorm Psychol* 2003;**112**(3):393–402.
61. Jones RT, Benowitz N, Bachman J. Clinical studies of cannabis tolerance and dependence. *Ann N Y Acad Sci* 1976;**282**:221–39.
62. Haney M, Ward AS, Comer SD, et al. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology* 1999;**141**(4):385–94.
63. Budney AJ, Hughes JR, Moore BA, et al. Marijuana abstinence effects in marijuana smokers maintained in their home environment. *Arch Gen Psychiatry* 2001;**58**(10):917–24.
64. Budney AJ, Vandrey RG, Hughes JR, et al. Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. *Drug Alcohol Depend* 2007;**86**(1):22–9.
65. Pivik RT, Zarcone V, Dement WC, et al. Delta-9-tetrahydrocannabinol and synhexl: effects on human sleep patterns. *Clin Pharmacol Ther* 1972;**13**(3):426–35.
66. Flynn PM, Kristiansen PL, Porto JV, et al. Costs and benefits of treatment for cocaine addiction in DATOS. *Drug Alcohol Depend* 1999;**57**:167–74.
67. French MT, Roebuck MC, Dennis ML, et al. The economic cost of outpatient marijuana treatment for adolescents: findings from a multi-site field experiment. *Addiction* 2002;**97**:S84–97.
68. Poling J, Kosten TR, Sofuoglu M. Treatment outcome predictors for cocaine dependence. *Am J Drug Alcohol Abuse* 2007;**33**(2):191–206.

69. Crowley TJ, Macdonald MJ, Whitmore EA, et al. Cannabis dependence, withdrawal, and reinforcing effects among adolescents with conduct symptoms and substance use disorders. *Drug Alcohol Depend* 1998;**50**(1):27–37.
70. Stephens RS, Babor TF, Kadden R, et al. The Marijuana Treatment Project: rationale, design and participant characteristics. *Addiction* 2002;**97**:109–24.
71. Gillin JC, Smith TL, Irwin M, et al. Increased pressure for rapid eye movement sleep at time of hospital admission predicts relapse in nondepressed patients with primary alcoholism at 3-month follow-up. *Arch Gen Psychiatry* 1994;**51**:189–97.
72. Brower KJ, Aldrich MS, Hall JM. Polysomnographic and subjective sleep predictors of alcoholic relapse. *Alcohol Clin Exp Res* 1998;**22**:1864–71.
73. Gann H, Feige B, Hohagen F, et al. Sleep and the cholinergic rapid eye movement sleep induction test in patients with primary alcohol dependence. *Biol Psychiatry* 2001;**50**(5):383–90.
74. Monnelly EP, Ciraulo DA, Knapp C, et al. Quetiapine for treatment of alcohol dependence. *J Clin Psychopharmacol* 2004;**24**(5):532–5.
75. Sofuoglu M, Kosten TR. Emerging pharmacological strategies in the fight against cocaine addiction. *Expert Opin Emerg Drugs* 2006;**11**(1):91–8.
76. Roberts DC. Preclinical evidence for GABA-B agonists as a pharmacotherapy for cocaine addiction. *Physiol Behav* 2005;**86**(1/2):18–20.
77. Haney M, Hart CL, Foltin RW. Effects of baclofen on cocaine self-administration: opioid- and nonopioid-dependent volunteers. *Neuropsychopharmacology* 2006;**31**(8):1814–21.
78. Dackis CA, Kampman KM, Lynch KG, et al. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *Neuropsychopharmacology* 2005;**30**(1):205–11.
79. Hart CL, Haney M, Vosburg SK, et al. Smoked cocaine self-administration is decreased by modafinil. *Neuropsychopharmacology*, in press.
80. Wesensten NJ. Effects of modafinil on cognitive performance and alertness during sleep deprivation. *Curr Pharm Des* 2006;**12**(20):2457–71.
81. Kruszewski SP. Euphorogenic and abusive properties of modafinil. *Am J Psychiatry* 2006;**163**(3):549.
82. O'Brien CP, Dackis CA, Kampman K. Does modafinil produce euphoria? *Am J Psychiatry* 2006;**163**(6):1109.
83. Voderholzer U, Hornyak M, Thiel B, et al. Impact of experimentally induced serotonin deficiency by tryptophan depletion on sleep EEG in healthy subjects. *Neuropsychopharmacology* 1998;**18**(2):112–24.
84. Bhatti T, Gillin JC, Seifritz E, et al. Effects of a tryptophan-free amino acid drink challenge on normal human sleep electroencephalogram and mood. *Biol Psychiatry* 1998;**43**(1):52–9.
85. Huwig-Poppe C, Voderholzer U, Backhaus J, et al. The tryptophan depletion test. Impact on sleep in healthy subjects and patients with obsessive-compulsive disorder. *Adv Exp Med Biol* 1999;**467**:35–42.
86. Voderholzer U, Riemann D, Huwig-Poppe C, et al. Sleep in obsessive compulsive disorder. Polysomnographic studies under baseline conditions and after experimentally induced serotonin deficiency. *Eur Arch Psychiatry Clin Neurosci* 2007;**257**(3):173–82.
87. Moore P, Gillin JC, Bhatti T, et al. Rapid tryptophan depletion, sleep electroencephalogram, and mood in men with remitted depression on serotonin reuptake inhibitors. *Arch Gen Psychiatry* 1998;**55**:534–9.
88. Riemann D, Feige B, Hornyak M, et al. The tryptophan depletion test: impact on sleep in primary insomnia—a pilot study. *Psychiatry Res* 2002;**109**(2):129–35.
89. Walther S, Mahlberg R, Eichmann U, et al. Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. *Psychopharmacology* 2006;**185**(4):524–8.
90. Lee PE, Gill SS, Freedman M, et al. Atypical antipsychotic drugs in the treatment of behavioural and psychological symptoms of dementia: systematic review. *BMJ* 2004;**329**(7457):75.
91. Daiello LA. Atypical antipsychotics for the treatment of dementia-related behaviors: an update. *Med Health R I* 2007;**90**(6):191–4.
92. Russo EB, Guy GW, Robson PJ. Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. *Chem Biodivers* 2007;**4**(8):1729–43.

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Using Cannabis To Help You Sleep: Heightened Frequency of Medical Cannabis Use among Those with PTSD

Marcel O. Bonn-Miller,

Center for Innovation to Implementation and National Center for PTSD, VA Palo Alto Health Care System 795 Willow Road, Menlo Park, California 94025-USA; Center of Excellence in Substance Abuse Treatment and Education, Philadelphia VAMC Department of Psychiatry, University of Pennsylvania

Kimberly A. Babson, and

Center for Innovation to Implementation, VA Palo Alto Health Care System Department of Psychiatry and Behavioral Sciences, Stanford School of Medicine 795 Willow Road, Menlo Park, California 94025-USA

Ryan Vandrey

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University 5510 Nathan Shock Drive, Baltimore, Maryland 21224-USA

Abstract

Background—The use of cannabis for medical purposes is proliferating in the U.S., and PTSD is an explicitly approved condition for accessing medical cannabis in 5 states. Prior research suggests that people with PTSD often use cannabis to help cope with their condition, and that doing so results in more frequent and problematic cannabis use patterns. Specific coping motivations, such as sleep improvement, among medical cannabis users, have not been examined.

Methods—The present study evaluated specific coping use motivations, frequency of cannabis and alcohol use, and mental health among a convenience sample of patients (N=170) at a medical cannabis dispensary in California.

Results—Those with high PTSD scores were more likely to use cannabis to improve sleep, and for coping reasons more generally, compared with those with low PTSD scores. Cannabis use frequency was greater among those with high PTSD scores who used for sleep promoting purposes compared with those with low PTSD scores or those who did not use for sleep promoting purposes.

Conclusions—Consistent with prior research, this study found increased rates of coping-oriented use of cannabis and greater frequency of cannabis use among medical users with high PTSD scores compared with low PTSD scores. In addition, sleep improvement appears to be a

Contact Information for Corresponding Author Marcel Bonn-Miller, 795 Willow Road, Menlo Park, CA 94025, USA. Phone: 650-493-5000; Fax: 650-617-2736; Marcel.Bonn-Miller@va.gov.

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Contributors Dr. Bonn-Miller designed the study and wrote the protocol. Drs. Bonn-Miller and Vandrey managed the literature searches and summaries of previous related work. Dr. Babson undertook the statistical analysis, method, and results. Dr. Bonn-Miller wrote the first draft of the manuscript. Dr. Vandrey provided editing and revisions to drafts. All authors contributed to and have approved the final manuscript.

Conflict of Interest All authors declare that they have no conflicts of interest.

primary motivator for coping-oriented use. Additional research is needed to examine the health consequences of this pattern of cannabis use and whether alternative sleep promoting interventions (e.g. CBT-I) could reduce the reliance on cannabis for adequate sleep among those with PTSD.

Keywords

cannabis; coping; medical marijuana; PTSD; sleep

1. INTRODUCTION

Cannabis is the most widely used illicit substance in the United States (SAMHSA, 2012) and the legalization of cannabis for medicinal purposes has become a growing trend. The approved conditions for which cannabis may be doctor-recommended varies at the state level, but most states allow medical use of cannabis for certain medical disorders/problems (e.g., cancer, severe and chronic pain, HIV/AIDS). The use of medical cannabis for psychological disorders, however, is not as common. Currently, only 5 of 20 states with medical cannabis laws explicitly allow the medical use of cannabis as a treatment for those with posttraumatic stress disorder (PTSD).

Though there has been a general dearth of empirical research speaking to the use and effects of cannabis among those with PTSD, existing evidence suggests that individuals with PTSD, particularly those with heightened hyperarousal symptoms, use cannabis primarily for coping reasons (e.g., Boden et al., 2013; Bonn-Miller et al., 2007a; Passie et al., 2012), and that such coping-oriented use may be associated with heavier and more problematic cannabis use patterns (e.g., dependence), as documented in the general population (Bonn-Miller and Zvolensky, 2009). Following, there has been increasing interest in understanding, among those with PTSD, the specific motives for which cannabis is used. In a study among 20 adult females with PTSD, Bonn-Miller and colleagues (2010) found poor sleep quality to interact with PTSD symptom severity in the prediction of coping-oriented cannabis use. Here, individuals with elevated PTSD symptoms and sleep problems were particularly likely to use cannabis to cope.

Though Bonn-Miller and colleagues (2010) documented the importance of sleep problems in terms of understanding the association between PTSD and coping-oriented cannabis use, little research has been conducted to examine whether specific symptoms of PTSD are being “treated” with cannabis use, and, in particular, whether individuals with PTSD use cannabis specifically to improve sleep, or instead to cope with negative affect more broadly. Here, recent work has demonstrated that specific psychoactive components of cannabis may initially facilitate sleep onset (Russo et al., 2007; Schierenbeck et al., 2008), though long-term and problematic use has been associated with sleep disturbances, including altered sleep architecture (Bolla et al., 2008; Vandrey et al., 2011). Additionally, there has yet to be an investigation of how specific coping motivations are associated with use frequency within this context.

The present study sought to examine (1) the specific cannabis motives that distinguish a medicinal cannabis-using individual with PTSD from an individual without PTSD, and (2) whether the interaction of PTSD and PTSD-specific use motives are associated with more severe use frequency. We hypothesized that medical cannabis users with PTSD would be more likely to report cannabis use specifically to improve sleep, compared to those without PTSD. Further, due to the development of tolerance to the sleep-inducing effects of cannabis (Schierenbeck et al., 2008), as well as prior documented associations between coping-oriented use and heavy cannabis use patterns (Bonn-Miller and Zvolensky, 2009), we hypothesized that those with PTSD who also used for sleep motives would evidence greater

cannabis use frequency. As research has demonstrated that depression and alcohol use are both associated with PTSD (McFarlane, 1998; Shalev et al., 1998) and cannabis use (Bovasso, 2001; Griffin et al., 2002), depressive symptoms and alcohol use were included as covariates.

2. METHOD

2.1 Participants

Study participants (N=217) were adult (18 and over) patients using cannabis obtained from a licensed medical cannabis dispensary in San Francisco, California. Of the participants enrolled in the study, 170 completed the requisite questionnaires and were included in data analyses. The mean age of the sample was 41 years ($SD=15$) and 22% were female. Participants were excluded based on inability to provide written informed consent to participate, and being under 18 years of age. The majority of participants self-identified as Caucasian (67.1%), followed by Black/Non-Hispanic (7.8%), Hispanic (7.8%), Black/Hispanic (3.0%), Asian (3.0%), and “Other” (11.4%). The most common self-reported conditions for which participants sought medical cannabis included anxiety (62.7%), chronic pain (55.6%), stress (47.9%), insomnia (47.9%), and depression (41.4%; see Bonn-Miller et al., 2013 for more complete description).

2.2 Procedure

Patients presenting to the medical cannabis dispensary were provided with the opportunity to participate in the study by research staff. After obtaining written informed consent to participate, interested individuals completed a battery of questionnaires. Research staff debriefed participants upon completion, and participants were entered into 1 of 4 drawings to receive a \$100 prize. Data describing self-reported cannabis use characteristics of this sample have been reported previously (Bonn-Miller et al., 2013). Study procedures were approved by the Stanford University IRB and conducted in accordance with the ethical principles of the Declaration of Helsinki.

2.3 Measures

2.3.1 Posttraumatic Stress—The PTSD Checklist-Civilian Version (PCL-C; Weathers et al., 1993) is a 17-item questionnaire in which respondents indicate presence and severity of symptoms of PTSD, derived from the DSM-IV symptoms for PTSD (APA, 2000). A total score was calculated. Consistent with recommendations among community samples (NCPTSD, 2013), a total score of 30 was used as a cut-off to generate two groups: those without PTSD (PCL score < 30) and those with probable PTSD (PCL score > 30). The PCL-C has excellent psychometric properties (Weathers et al., 1993). Cronbach’s $\alpha = .95$ in the current sample.

2.3.2 Cannabis Use Motives—The Comprehensive Marijuana Motives Questionnaire (CMMQ; Lee et al., 2009) was used to index motives for cannabis use. Participants rate how often they use cannabis for each of 36 reasons on a 5-point Likert-type scale (1 = “Almost Never/Never” to 5 = “Almost Always/Always”). These 36 items comprise 12 different domains (3 reasons/domain) of motives for use including: Enjoyment, Conformity, Coping (e.g., “To forget your problems”), Experimentation, Boredom, Alcohol, Celebration, Altered Perception, Social Anxiety, Low Risk, Sleep (e.g., “To help you sleep”), and Availability. Cronbach’s $\alpha = .74$ for CMMQ subscales in the current sample.

2.3.3 Cannabis Use Frequency—A single item from the Marijuana Smoking History Questionnaire (MSHQ; Bonn-Miller and Zvolensky, 2009) was used to determine past 30-day cannabis use, regardless of use motive (e.g., medicinal). Participants were asked to rate

the frequency of their cannabis use in the past 30 days on a scale of 0 “no use” to 8 “more than once a day.” The MSHQ has performed well in previous research, with convergent validity for the employed frequency item (Bonn-Miller and Zvolensky, 2009; Bonn-Miller et al., 2007b). In the present sample, scores ranged from 2-8 ($M = 7.09$, $SD = 1.37$).

2.3.4 Alcohol Use—The Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993) is a 10-item self-report measure of hazardous and harmful alcohol consumption. A total score is calculated to produce a global measure of problematic alcohol use. Cronbach’s $\alpha = .84$ in the current sample.

2.3.5 Depressive Symptoms—The Inventory of Depression and Anxiety Scale (IDAS; Watson et al., 2007) is a 64-item questionnaire measuring depression and anxiety. The General Depression subscale was employed as a measure of depressive symptoms and used as a covariate. Cronbach’s $\alpha = .84$ in the current sample.

2.4 Data Analysis

First, a series of t-tests were conducted to examine group (no PTSD versus probable PTSD) differences in terms of cannabis use motives. T-tests were adjusted ($p = .01$) for multiple comparisons. Next, we examined the interaction of motive for use (sleep and coping) and group on past 30-day cannabis use. Two separate hierarchical multiple regressions (HMRs) were conducted (one for sleep, one for coping motives) in which past 30-day cannabis use served as the outcome variable. Sleep and coping motives were selected, as these were the only two motives that were found to vary as a function of PTSD symptom levels. All continuous variables were standardized prior to entry. In Step 1, main effects for motive (sleep or coping) and PTSD group were simultaneously entered. In step 2, the interaction between motive (sleep or coping) and PTSD group was entered. In step 3, alcohol use (AUDIT total score) and depressive symptoms (IDAS General Depression sub-score) were entered as covariates. Variables were entered in this fashion to test whether the obtained results remained after adjusting for relevant covariates, while ensuring that interaction effects were not significant merely due to suppression effects of covariates (Simmons et al., 2011).

3. RESULTS

Results of t-tests indicated that individuals with probable PTSD reported greater motivation to use cannabis for sleep and coping reasons compared to those without PTSD. No associations were found between PTSD and any other motives (see Table 1). In the hierarchical regressions (see Table 1), a significant main effect for sleep motives, but not PTSD group, was observed in predicting past 30-day cannabis use. Furthermore, as predicted, the interaction between sleep motives and group was associated with past 30-day cannabis use, accounting for 3% of unique variance. After adjusting for covariates in Step 3, the interaction remained significant with the entire model accounting for 25.2% of variance in past 30-day cannabis use. In terms of coping motives, there was a main effect for coping, but not PTSD group. In addition, the interaction of PTSD group and coping was non-significant.

Consistent with recommendations for examining interactions (Aiken and West, 1991), post-hoc probing of the significant interaction indicated that sleep motives was positively associated with past 30-day cannabis use among individuals with probable PTSD, but not among individuals without PTSD (see Figure 1).

Analyses were also run using a continuous index of PTSD symptoms (total PCL score). Results remained consistent. A significant interaction of sleep motive and PTSD symptoms

emerged both before, $\beta = .70, p = .008$, and after, $\beta = .69, p = .009$, accounting for covariates. In addition, analyses related to coping motives still yielded a non-significant interaction, $\beta = -.07, p = .80$.

4. DISCUSSION

The present study sought to extend prior work by determining motivation for cannabis use among individuals who report elevated PTSD symptoms and use medical cannabis. First, the present study replicated prior work (e.g., Bonn-Miller et al., 2007a; 2013) by documenting that individuals with probable PTSD used cannabis for negative affect reduction (i.e., coping motives). Consistent with hypotheses, the present study also provided the first empirical evidence for cannabis use for sleep reasons among those with probable PTSD, with these two motives (i.e., coping, sleep) being the only motives observed to differ between those with probable PTSD and those without.

Also consistent with expectation, PTSD group was found to interact with sleep motives in terms of cannabis use frequency. These findings extend prior work that documented an interactive relation between PTSD symptoms and sleep problems in terms of coping motives (Bonn-Miller et al., 2010) by showing that those with probable PTSD (and those with greater PTSD symptom severity) who used cannabis to improve sleep reported more frequent cannabis use. Indeed, no association was observed between sleep motives and use frequency among the non-PTSD group. Though coping-oriented use was elevated among those with probable PTSD, no interaction was observed for frequency of cannabis use, providing strong evidence for the uniqueness of the association between PTSD symptoms and sleep motives in terms of cannabis use frequency. Finally, all of the aforementioned associations were observed above and beyond co-occurring alcohol problems and depressive symptoms, and among a sample of medicinal cannabis users, a group heretofore unexamined in terms of PTSD and associated use motivation.

Though the present study provides strong empirical evidence for the unique role of sleep-motivated cannabis use among medicinal cannabis users with probable PTSD, it is not without limitation. First, the present study was cross-sectional in nature. Additionally, it was conducted within one cannabis dispensary in San Francisco, and the sample was primarily male. So as to improve our understanding of the observed associations and generalizability of findings, future work should employ prospective assessment among samples more representative of the medicinal cannabis using population. Another limitation of the present study was that no interview-based or objective measures were employed (all data were self-report). Though the employed measures were well validated and have been used extensively in prior literature, future work would benefit from including biochemical verification of cannabis use status as well as behavioral (e.g., cue exposure) and/or interview-based (e.g., Clinician Administered PTSD Scale; Blake et al., 1995) measures of PTSD status and symptomatology.

Limitations notwithstanding, the present study provides empirical evidence to suggest that individuals with high levels of PTSD symptoms use medicinal cannabis for coping and sleep motives, and that sleep-motivated use, specifically, is associated with more frequent cannabis use. Interventions shown to improve sleep quality (e.g., Cognitive Behavioral Therapy for Insomnia; Morin et al., 2006) may be useful in terms of providing an alternative to cannabis for individuals with PTSD who are reporting significant difficulties with sleep. It is unknown whether the high rate of cannabis use among this sub-population is associated with adverse health outcomes relative to those with PTSD who do not use cannabis.

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REFERENCES

- Aiken, L.; West, S. *Multiple Regression: Testing and Interpreting Interactions*. Sage; Newbury Park, CA: 1991.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th Edition – Text Revision. American Psychiatric Association; Washington, DC: 2000.
- Blake D, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM. The development of a clinician-administered PTSD scale. *J. Trauma Stress*. 1995; 8:75–90. [PubMed: 7712061]
- Boden MT, Babson KA, Vujanovic AA, Short NA, Bonn-Miller MO. Posttraumatic stress disorder and cannabis use characteristics among military veterans with cannabis dependence. *Am. J. Addict*. 2013; 22:277–284. [PubMed: 23617872]
- Bolla K, Lesage S, Gamaldo C, Neubauer D, Funderbuck F, Lud Cadet J, David PM, Verdejo-Garcia A, Benbrook AR. Sleep disturbance in heavy marijuana users. *Sleep*. 2008; 31:901–908. [PubMed: 18548836]
- Bonn-Miller MO, Babson KA, Vujanovic AA, Feldner MT. Sleep problems and PTSD symptoms interact to predict marijuana use coping motives: a preliminary investigation. *J. Dual Diagnosis*. 2010; 6:111–122.
- Bonn-Miller MO, Boden MT, Bucossi MM, Babson KA. Self-reported cannabis use characteristics, patterns, and helpfulness among medical cannabis users. *Am. J. Drug Alcohol Abuse*. 2013 Epub ahead of print.
- Bonn-Miller MO, Vujanovic AA, Feldner MT, Bernstein A, Zvolensky MJ. Posttraumatic stress symptom severity predicts marijuana use coping motives among traumatic event-exposed marijuana users. *J. Trauma Stress*. 2007a; 20:577–586. [PubMed: 17721963]
- Bonn-Miller MO, Zvolensky MJ. An evaluation of the nature of marijuana use and its motives among young adult active users. *Am. J. Addict*. 2009; 18:409–416. [PubMed: 19874161]
- Bonn-Miller MO, Zvolensky MJ, Marshall E. Incremental validity of anxiety sensitivity in relation to marijuana withdrawal symptoms. *Addict. Behav*. 2007b; 32:1843–1851. [PubMed: 17236723]
- Bovasso G. Cannabis abuse as a risk factor for depressive symptoms. *Am. J. Psychiatry*. 2001; 158:2033–2037. [PubMed: 11729021]
- Griffin K, Botvin G, Scheier L, Nichols T. Factors associated with regular marijuana use among high school students: a long-term follow-up study. *Subst. Use Misuse*. 2002; 37:225–238. [PubMed: 11863277]
- Lee CM, Neighbors C, Hendershot CS, Grossbard JR. Development and preliminary validation of a comprehensive marijuana motives questionnaire. *J. Stud. Alcohol Drugs*. 2009; 70:279–287. [PubMed: 19261240]
- McFarlane A. Epidemiological evidence about the relationship between PTSD and alcohol abuse: the nature of the association. *Addict. Behav*. 1998; 23:813–825. [PubMed: 9801718]
- Morin C, Bootzin R, Buysse D, Edinger J, Espie C, Lichstein K. Psychological and behavioral treatment of insomnia: update of the recent evidence (1998-2004). *Sleep*. 2006; 29:1398–1414. [PubMed: 17162986]
- National Center for PTSD. [Retrieved on 9/15/2013] Using the PTSD Checklist (PCL). <http://www.ptsd.va.gov/professional/pages/assessments/assessment-pdf/pcl-handout.pdf>
- Passie T, Emrich HM, Karst M, Brandt SD, Halpern JH. Mitigation of post-traumatic stress symptoms by cannabis resin: a review of the clinical and neurobiological evidence. *Drug Test Anal*. 2012; 4:649–659. [PubMed: 22736575]

- Russo EB, Guy GW, Robson PJ. Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. *Chem. Biodivers.* 2007; 4:1729–1743. [PubMed: 17712817]
- Saunders J, Aasland O, Babor T, de la Fuente J, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction.* 1993; 88:791–804. [PubMed: 8329970]
- Schierenbeck T, Riemann D, Berger M, Homyak M. Effect of illicit recreational drugs upon sleep: cocaine, ecstasy and marijuana. *Sleep Med. Rev.* 2008; 12:381–389. [PubMed: 18313952]
- Shalev A, Freedman S, Peri T, Brandes D, Sahar T, Orr S, Pitman R. Prospective study of posttraumatic stress disorder and depression following trauma. *Am. J. Psychiatry.* 1998; 155:630–637. [PubMed: 9585714]
- Simmons J, Nelson L, Simonsohn U. False-positive psychology: undisclosed flexibility in data collection and analysis allows presenting anything as significant. *Psychol. Sci.* 2011; 22:1359–1366. [PubMed: 22006061]
- Substance Abuse and Mental Health Services Administration. Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-44, HHS Publication No. (SMA) 12-4713. Substance Abuse and Mental Health Services Administration; Rockville, MD: 2012.
- Vandrey R, Smith MT, McCann UD, Budney AJ, Curran EM. Sleep disturbance and the effects of extended release zolpidem during cannabis withdrawal. *Drug Alcohol Depend.* 2011; 117:38–44. [PubMed: 21296508]
- Watson D, O'Hara M, Simms L, Kotov R, Chmielewski M, McDade-Montez E, Gamez W, Stuart S. Development and validation of the Inventory of Depression and Anxiety Symptoms (IDAS). *Psychol. Assess.* 2007; 19:253–268. [PubMed: 17845118]
- Weathers, F.; Litz, B.; Herman, D.; Huska, J.; Keane, T. The PTSD Checklist (PCL): Reliability, Validity, and Diagnostic Utility. Paper presented at the Annual Convention of the International Society for Traumatic Stress Studies; San Antonio, TX. 1993.

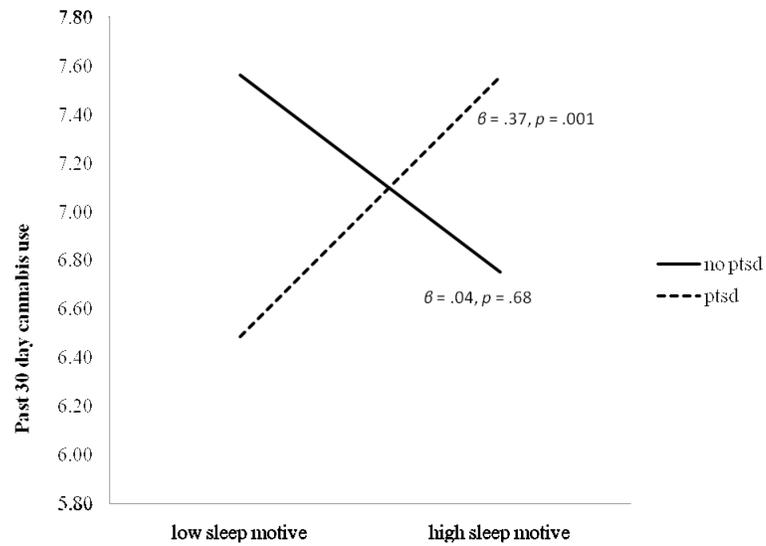


Figure 1. Level of past 30-day cannabis use as a function of the interaction between PTSD group (no PTSD versus Probable PTSD) and sleep motives. Frequency of past 30-day cannabis use was ranked on a scale of 0 “no use” to 8 “more than once a day”.



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An Analysis of Applicants Presenting to a Medical Marijuana Specialty Practice in California

Helen Nunberg, MD, MPH, Beau Kilmer, PhD, Rosalie Liccardo Pacula, PhD, and James Burgdorf

Abstract

For more than a decade, medical marijuana has been at the forefront of the marijuana policy debate in the United States. Fourteen states allow physicians to recommend marijuana or provide a legal defense for patients and physicians if prosecuted in state courts; however, little is known about those individuals using marijuana for medicinal purposes and the symptoms they use it for. This study provides descriptive information from 1,655 patients seeking a physician's recommendation for medical marijuana, the conditions for which they seek treatment, and the diagnoses made by the physicians. It conducts a systematic analysis of physician records and patient questionnaires obtained from consecutive patients being seen during a three month period at nine medical marijuana evaluation clinics belonging to a select medical group operating throughout the State of California. While this study is not representative of all medical marijuana users in California, it provides novel insights about an important population being affected by this policy.

I. INTRODUCTION

As of December 2010, 15 states and the District of Columbia provide allowances for medical marijuana (National Conference of State Legislatures, 2010).¹ There is a small literature about whether these laws influence the overall demand for marijuana (Gorman and Charles, 2007; Pacula et al., 2010), and a tremendous amount of discussion about how medicinal marijuana is distributed, especially in California (see e.g., Hoeffel, 2010a; 2010b). What remains largely missing from the literature and policy discussions is a good understanding of the individuals who seek a medical allowance for marijuana.

This paper helps fill this gap by systematically evaluating the characteristics, ailments, and medical histories of a large group of applicants seeking a medicinal marijuana recommendation. Data are collected from medical charts and doctor interviews with 1,655 individuals seen in June, July and August of 2006 from nine medical marijuana specialty practices dispersed throughout California. The results provide some interesting insights as to the characteristics of those seeking medicinal allowances nearly a decade after the policy was introduced in California.

The remainder of this paper is organized as follows. In Section 2 we briefly review the literature on the therapeutic value of cannabinoids, provide details of the specific allowances provided for within California state law, and review previously published surveys of populations of medical marijuana users. In Section 3 we discuss the methods that were used in the current study, including our data collection procedures, and in Section 4 we present

¹This excludes Maryland. While Maryland does allow those arrested for marijuana possession to use a medical necessity defense, those found to be using for medical purposes are still convicted and can be fined up to \$100.

our results. A general discussion of these findings and the limitations of our study are presented in Section 5.

II. BACKGROUND AND LITERATURE REVIEW

Research on the therapeutic value of cannabinoids

Cannabinoids are compounds related to tetrahydrocannabinol (THC) found in the cannabis plant (phytocannabinoids), in animals (endocannabinoids), and synthesized in laboratories (e.g., THC analogues, cannabinoid receptor agonists and antagonists) (Pertwee, 2006). Cannabinoid receptors are found in all animals; in humans, cannabinoid receptors are concentrated in the brain but are also found in other parts of the body.

The use of cannabis as a medicine originated thousands of years ago. After being introduced to the West in the mid-nineteenth century, cannabis-based medicines were popular through the early decades of the twentieth century (Grinspoon, 2005; Zuardi, 2006). The virtual disappearance of cannabis-based medicines by the mid-1900s was due to the introduction of new pharmaceuticals (e.g., aspirin, chloral hydrate, barbiturates) for the same conditions, such as pain, migraines, menstrual cramps, and sedation, as well as the legal restrictions associated with the 1937 Marijuana Tax Act (Fankhauser, 2002; Grinspoon).

The Institute of Medicine's (IOM) 1999 report *Marijuana and Medicine: Assessing the Science Base*, concluded that "Scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily THC, for pain relief, control of nausea and vomiting, and appetite stimulation; smoked marijuana, however, is a crude THC delivery system that also delivers harmful substances" (4). The report further noted that, "For the most part, the logical categories for the medical use of marijuana are not based on particular diseases but on symptoms...[that] can be caused by various diseases or even by treatments for diseases" (IOM, 1999; pp. 137–138). Based on these findings, the panel recommended that "clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems" (4). In addition to focusing on pain relief, control of nausea and vomiting, and appetite stimulation, the IOM report also called recommended that clinical trials focus on the suitability of cannabinoid drugs to address anxiety reduction and sedation.

Reviews published since the IOM report also highlight the potential therapeutic value of cannabinoid drugs; however, few of the studies focus on inhaled marijuana. A review of 72 randomized, double-blind, placebo-controlled studies from 1975 to 2004 evaluating the therapeutic effects of cannabinoids concludes that "Cannabinoids present an interesting therapeutic potential as antiemetics, appetite stimulants in debilitating diseases (cancer and AIDS), analgesics, and in the treatment of multiple sclerosis, spinal cord injuries, Tourette's syndrome, epilepsy and glaucoma" (Ben Amar, 2006). A more recent review focusing on clinical studies published from 2005 to 2009 (Hazekamp and Grotenhermen, 2010) concluded that cannabinoids have "therapeutic potential mainly as analgesics in chronic neuropathic pain, appetite stimulants in debilitating diseases (cancer and AIDS), as well as in the treatment of multiple sclerosis." For both reviews, a minority of the trials evaluated inhaled marijuana (six and eight studies, respectively). The others used a synthetic THC isomer or analog for oral administration, or plant extract in oral or sublingual preparations.²

²Hazekamp and Grotenhermen included recent studies of nabilone, a prescription drug that is a THC analog. Skrabek et al. (2008) performed a randomized, controlled trial to assess the benefit of nabilone on pain reduction and quality of life improvement in patients with fibromyalgia. They found significant decreases in pain and anxiety. Similarly, Ware et al. (2010) concluded that nabilone "is effective in improving sleep in patients with fibromyalgia and is well tolerated." Finally, in a more recent observational study (Bestard and Toth, 2010), nabilone was found to be as effective as gabapentin, a first line medication for peripheral neuropathy, in measures of pain, sleep, depression and anxiety.

In February 2010, the Center for Medicinal Cannabis Research (CMCR) at the University of California San Diego submitted a report to the Legislature and Governor of California describing five completed clinical trials with inhaled marijuana (Grant et al., 2010). Four demonstrated pain relief effects in conditions secondary to injury or disease of the nervous system (Abrams et al., 2007; Wallace et al., 2007; Wilsey et al., 2008; Ellis et al., 2009), and one suggested a reduction of spasticity in multiple sclerosis (Corey-Bloom et al., 2008).

Medicinal Marijuana in California

In California, patients with a physician's recommendation, along with their designated caregivers and recommending physicians, are exempted from state criminal laws against marijuana. Although provision and use remain illegal under federal law, U.S. Attorney General Eric Holder made a statement in March 2009 suggesting that the federal government would not target those who complied with state medical marijuana laws. This was made more official in an October 2009 memo to U.S. Attorneys which noted that: "As a general matter, pursuit of these priorities should not focus federal resources in your States on individuals whose actions are in clear and unambiguous compliance with existing state laws providing for the medical use of marijuana."

The California medical marijuana law, passed through voter referendum (Proposition 215) in 1996, permits the use of marijuana for "cancer, anorexia, AIDS, chronic pain, spasticity, glaucoma, arthritis, migraine, *or any other illness for which marijuana provides relief*" [emphasis added]. California Senate Bill 420, signed into law on October 12, 2003, named additional ailments such as severe nausea, cachexia, seizures, and persistent muscle spasms (regardless of whether they are associated with multiple sclerosis). In an effort to provide better guidance to law enforcement agencies, SB 420 allowed patients and primary caregivers to possess up to six mature plants (or 12 immature plants) and eight ounces of marijuana; however, it granted local governments the authority to establish larger maximum quantities.

Many of the early studies about medicinal marijuana users in California focused on individuals with HIV or AIDS (e.g., Harris et al., 2000; Sidney, 2001; de Jong et al., 2005; Prentiss et al., 2004). Based on analyses of several unpublished surveys of clients entering cannabis buyer clubs in the San Francisco Bay Area, Gieringer (2002) found that the share of clients that were AIDS and cancer patients declined after the passage of Proposition 215. More recent research in California shows that medicinal marijuana patients are largely men who present with pain and/or emotional/mental health concerns (O'Connell and Bou-Matar, 2007; Reiman, 2007; Reiman, 2009). An informal survey of several California medical marijuana specialty physicians revealed that more than 95% of the patients of each physician were already "self-medicating" prior to the receipt of their recommendation, leading Mikuriya et al. (2007) to conclude that the physicians were really "approving" the medical use of marijuana as opposed to "recommending" it.

III. DATA AND METHODS

The data used in this study come from medical records of 1,745 applicants consecutively presenting to one of nine MediCann clinics located in large and small cities throughout California.³ The sample is based on visits in June, July, and August 2006, roughly ten years after the original law was enacted. Medical charts were reviewed and data entered within a few weeks of the visit. Our final sample excludes 90 individuals who are either missing diagnosis information (N=35) or did not report using marijuana before seeking a

³Since 2006, MediCann has expanded to 21 locations throughout California.

recommendation (N=55).⁴ There are no statistically significant differences in terms of age, race/ethnicity, and gender between those included and excluded in the analysis sample.

We drew on consecutive visits from all nine clinics in hopes of approximating a representative sample of applicants seeking recommendations at these medical marijuana specialty practices. The sample is not generalizable to all individuals applying for a medical marijuana recommendation as it only represents those individuals selecting this particular network of physicians.

In general, the MediCann policy was to provide a 12-month recommendation to those with an acceptable medical condition who had supporting medical record documentation.⁵ Those without medical record documentation received a provisional three-month recommendation conditional upon them providing the MediCann physician with a copy of the relevant supporting medical record, or, if not currently under the care of a medical professional, seeking care and providing those records. Applicants were only denied if they did not report having an eligible medical condition or if they refused to be under the care of a medical professional. For our sample the denial rate was less than 2%.

MediCann's medical records include two standard forms specifically created for MediCann. One form is filled out by the applicant and includes demographic information, medical history, and marijuana use history. The second form is filled out by the evaluating physician and contains clinical information related to the health problem and symptoms for which the applicant is seeking help. Clinic physicians relied on medical histories, physical exams, and the supporting medical documents when they assigned diagnoses. The supporting medical documents included laboratory and radiological evaluations to validate applicant claims of use of marijuana for relief of symptoms due to a medical condition. Over two-thirds of applicants (67.8%) brought medical record documentation with them at the time of the visits analyzed in our study.

In light of the limited information on this population of interest, we examine simple means or sample proportions for several variables of interest, including patient characteristics and stated therapeutic needs, physician diagnoses, and medical history. Results are provided for the entire sample and then broken down by gender.

IV. RESULTS

Applicant Characteristics

Applicant demographic information is shown in Table 1 both for the full sample and by gender, since almost 73% of the applicants seeking a recommendation were male. This is not much different than the share of those in the 2006 National Household Survey on Drug Use and Health who reported purchasing marijuana in the previous month (70%). Female applicants seeking recommendations were, on average, older and more likely than men to be African American, have some college education, have Medicaid (MediCal) health insurance, or to be unemployed and disabled (19.5% of women reported being unemployed due to disability). In general, those seeking recommendations were insured (73.0% currently insured, of whom 24.2% were covered through Medicare or Medicaid), have at least a high school degree (only 8.8% have less than a high school degree), and are generally employed (68.7%).

⁴While in many ways the applicants who report not using marijuana prior to seeking this recommendation are perhaps the most interesting, there are an insufficient number of these individuals in our sample for robust comparisons.

⁵Qualifying patients would be given a recommendation and would be reassessed periodically to review the course of treatment and any new information about their health, as well as to monitor response to treatment as indicated by a decrease in symptoms, an increase in level of function, or an improvement in quality of life.

As for the age distribution, at least half of the population seeking medical recommendations through this physician group was over the age of 35. For comparison, the median age for those 18 and older in the 2006 NSDUH who reported purchasing marijuana in the previous month was in the 26–29 year old category (those over 21 are placed into age categories).

Applicants' Self Reports of the Therapeutic Benefits of Marijuana

In light of the IOM's argument that the "logical categories for the medical use of marijuana are not based on particular diseases but on symptoms (IOM; pp. 137–138), we examined the self-reported therapeutic benefit received from marijuana and the symptoms it helped relieve. Applicants were asked "Which of the following best describe the therapeutic benefit you receive from medicinal cannabis? (Check the most important reasons you use cannabis.)" The results are presented in Table 2.

Applicants most frequently reported using medical marijuana for pain relief (82.6%), improved sleep (70.6%), and relaxation (55.6%). The next most frequently reported benefits included relief of muscle spasms (41.3%), headache (40.8%), relief of anxiety (38.1%), improved appetite (38.0%), relief of nausea and vomiting (27.7%), and relief of depression (26.1%). Half the applicants (50.8%) reported using marijuana as a substitute for prescription medication and 13.2% reported using marijuana as a substitute for alcohol.

Interestingly, women were statistically more likely than men to report that they used marijuana to relieve most of the indications listed, including headaches, anxiety, nausea, depression, panic, and medication side-effects. The only indication for which men were more likely than women to report use of marijuana was to help with focus. One in four men reported that marijuana improved focus.

Physician Diagnosis

Table 3 presents the highest frequency diagnoses and the diagnoses specifically listed in the Compassionate Use Act. Recall that treating physicians make their diagnoses based on a review of applicant's history, the medical records from treating physicians (in two-thirds of the cases), and on their own physical examination. Evaluating physicians were then asked to "circle only diagnoses related to patient's medicinal marijuana use" from a list of 162 diagnoses.

In general, chronic pain disorders were the most common diagnoses made by physicians, with nearly 60 percent (58.2%) of applicants being diagnosed with some sort of musculoskeletal or neuropathic chronic pain condition. Low back pain was diagnosed for over one quarter (26.2%) of patients seen during this three month period, with lumbar and cervical degenerative disc disease (together 21.8%) and arthritis (18%) the next most common diagnoses in the chronic pain group. Mental health disorders were the next largest group of diagnoses made (22.9%), followed closely by sleep disorders (21.3%). Diagnoses in the grouping "neurological disorders," including migraine and other headache, were made in 16.6% of applicants. Only 3% of the applicants were diagnosed with either cancer or HIV/AIDS.

Previous Treatments and Physician's Recommendations for Additional Treatment

Because self-reported information was collected from applicants and most provided medical documentation from their treating physician that could be reviewed by the evaluating physician, it was possible to consider the extent to which previous therapies had been used to cope with or treat the primary symptoms for which they were seeking a medical allowance. In Table 4 we provide a list of therapies or approaches that were previously tried or currently being used. Almost half of the applicants (47.6%) reported taking prescription

medication at the time of their evaluation, and nearly 4 out of 5 (79.5%) reported having taken prescription medication in the past for their problems. As chronic pain was the leading diagnosis for which marijuana was being recommended, we were curious to see what percent of applicants had used opioids or opiate medication to deal with their problem. On the physician evaluation form, evaluating physicians were asked to check yes or no if the applicant was currently using or had used in the past opioids or opiate medication prescribed by another physician for their chronic pain. Evaluating physicians determined that almost half of all applicants (48.0%) experiencing chronic pain either currently or in the past had been prescribed opioids or opiate medication.

Non-prescription therapies tried by applicants seeking medicinal marijuana allowances included physical therapy (48.6%), chiropractic services (37.2%), surgery (21.9%), psychological counseling (20.7%), and acupuncture (19.6%). Thus, these data do not suggest that applicants immediately seek marijuana recommendations as the first strategy to deal with their symptoms. In many cases, these individuals tried more traditional forms of medicine.

V. DISCUSSION

This study provides descriptive information from 1,655 applicants seeking a physician's recommendation for medical marijuana in California, the conditions for which they sought treatment, and the diagnoses made by the physicians. The most common diagnoses reported were for chronic pain, mental health conditions (primarily anxiety and depression), and sleep disorders (insomnia). For physicians who make medical marijuana recommendations, the risk of being deceived is not dissimilar to the risk of deception faced by those who prescribe oxycodone and other painkillers; however, those prescribing the latter can limit the number of pills and refills.⁶ For medical marijuana, existing laws and policies only allow physicians to distribute recommendations, they cannot control the number of purchases, what is purchased (e.g., % THC or other cannabinoid content), where it is purchased, or the route of administration (e.g., inhale smoke or vapor, ingest an edible, apply topically).

The majority of applicants reported that they tried other therapies, including prescription drugs, to manage their symptoms prior to seeking the medicinal allowance. Fifty percent of the sample reported that they used marijuana as a substitute for prescription medicine. This is consistent with other studies (e.g., Reiman, 2007; 2009) and raises important questions about the specific drugs they are replacing. Future research with this population should focus on previous and concurrent prescription medication use to examine claims that marijuana enables people to reduce or eliminate their use of prescription medications. These data could also be useful for understanding whether there could be cost-savings associated with substituting certain prescription medicines with marijuana.

This also raises the issue about whether the legalization of marijuana for non-medicinal purposes would influence the consumption of prescription drugs. Not only would legalization increase availability and reduce the price of marijuana (Kilmer et al., 2010), but the reduced stigma may increase the likelihood that some individuals try it for medicinal purposes. It could also be the case that doctors may be more willing to discuss marijuana use with patients if it was not prohibited.

Less than 5% of the applicants in our sample were diagnosed with HIV/AIDS, cancer, or glaucoma. While these were not the only diseases/conditions discussed when Proposition

⁶However, doctors prescribing oxycodone cannot prevent patients from crushing the pill to deactivate the time-release functionality and then snorting or injecting it.

215 was on the ballot, they did receive a lot of attention. This is not surprising; we would expect the number of applicants presenting with HIV/AIDS, cancer, or glaucoma to be relatively low compared to the number presenting with pain, anxiety, and insomnia, due to the relative prevalence of these conditions in the general population. However, it is also important to note that many of those receiving recommendations did so for conditions other than those listed by the IOM (pain relief, control of nausea and vomiting, and appetite stimulation).

Finally, the age profile observed in the sample of applicants is intriguing, especially when compared with those who report purchasing marijuana in the previous month in the 2006 NSDUH. One should not assume the larger median age for these applicants is statistically meaningful in light of the potential non-representativeness of our sample and the fact that it is drawn exclusively from California. However, if these age differences appear in future studies, it could offer important insights about age-related risk aversion and/or age-specific access to distribution networks—each with different policy implications. Thus, future work should explore the robustness of these differences and consider their implications for policy.

We conclude by reminding readers that we did not examine randomly-selected representative sample of all individuals in California seeking a medical recommendation for the use of marijuana. We were merely able to collect data from a sample of individuals who presented themselves within a three month window to a group of doctors that they most likely expected would be willing to provide them with a recommendation. The applicants receiving recommendations from these doctors may differ from those in the general population in important ways that we are unable to know. As applicants receiving physician recommendations are not required by law to register with county or state health officials, we have no way of knowing the extent to which the population served by this particular physician group might differ from that served by other medical marijuana specialists or by primary care physicians. Knowledge about the number and type of individuals that receive recommendations from other specialists or from primary care physicians would improve our understanding medical marijuana users in California.

Since California law allows for medical marijuana use for any “illness for which marijuana provides relief,” we have an enormous opportunity to further our understanding of the risks and benefits of marijuana with careful questioning of some of the thousands of patients willing to discuss their use of marijuana. Detailed information about the doses, frequency, methods, and forms of marijuana consumed, as well as information about past and present alcohol, illicit drug, and prescription drug consumption would be of great interest.

VI. REFERENCES

- Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology*. 2007; 68(7):515–521. [PubMed: 17296917]
- Ben Amar M. Cannabinoids in medicine: A review of their therapeutic potential. *Journal of Ethnopharmacology*. 2006; 105(1–2):1–25. [PubMed: 16540272]
- Bestard JA, Toth CC. An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. *Pain Practice*. 2010 Nov 18. (Epub ahead of print).
- Corey-Bloom, J.; Wolfson, T.J.; Gamst, A.C.; Jin, S.; Marcotte, T.; Bentley, H., et al. Short-term effects of medicinal cannabis on spasticity in multiple sclerosis. Presented at the 60th Annual Meeting of the American Academy of Neurology; Chicago, IL. 2008 Apr 12–19.
- Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology*. 2009; 34(3):672–680. [PubMed: 18688212]

- Fankhauser, M. History of cannabis in Western medicine. In: Grotenhermen, F.; Russo, E., editors. Cannabis and cannabinoids: pharmacology, toxicology, and therapy. New York: Haworth Press; 2002. p. 37-50.
- Grant, I.; Atkinson, JH.; Mattison, A.; Coates, TJ. Report to the legislature and governor of the state of California presenting findings pursuant to SB847 which created the CMCR and provided state funding. San Diego, CA: University of California, San Diego; 2010.
- Gieringer, D. Medical use of cannabis: Experience in California. In: Grotenhermen, F.; Russo, E., editors. Cannabis and cannabinoids: pharmacology, toxicology, and therapy. New York: Haworth Press; 2002. p. 143-152.
- Gorman DM, Charles HJ. Do medical cannabis laws encourage cannabis use? *International Journal of Drug Policy*. 2007; 18(3):160–167. [PubMed: 17689362]
- Grinspoon, L. History of cannabis as medicine. DEA statement, prepared for DEA Administrative Law Judge hearing beginning. Aug 22. 2005 Retrieved July 28, 2010, from http://www.maps.org/mmj/grinspoon_history_cannabis_medicine.pdf
- Harris D, Jones RT, Shank R, Nath R, Fernandez E, Goldstein K, et al. Self-reported marijuana effects and characteristics of 100 San Francisco medical marijuana club members. *Journal of Addictive Diseases*. 2000; 19(3):89–103. [PubMed: 11076122]
- Hazekamp A, Grotenhermen F. Review on clinical studies with cannabis and cannabinoids 2005–2009. *Cannabinoids*. 2010; 5(special issue):1–21.
- Hoeffel, J. L.A. orders 439 medical marijuana dispensaries to close. *Los Angeles Times*; 2010a May 5.
- Hoeffel, J. Oakland approves ordinance to permit industrial marijuana production. *Los Angeles Times*; 2010b Jul 22.
- Institute of Medicine (IOM). Marijuana and medicine: Assessing the science base. Washington, DC: National Academy Press; 1999.
- de Jong BC, Prentiss D, McFarland W, Machekano R, Israelski DM. Marijuana use and its association with adherence to antiretroviral therapy among HIV-infected persons with moderate to severe nausea. *Journal of Acquired Immune Deficiency Syndromes*. 2005; 38(1):43–46. [PubMed: 15608523]
- Kilmer, B.; Caulkins, JP.; Pacula, RL.; MacCoun, R.; Reuter, PH. Altered state? Assessing how marijuana legalization in California could influence marijuana consumption and public budgets (No. OP-315-RC). Santa Monica: RAND Corporation; 2010.
- Mikuriya T, Hergenrather J, Denney P, Lucido F, Bearman D, Nunberg H. Medical marijuana in California, 1996–2006. *O’Shaughnessy’s*. 2007 Winter-Spring;:1,4–8. 41–43.
- National Conference of State Legislatures (NCSL). State medical marijuana laws. 2010. Retrieved December 9, 2010, from <http://www.ncsl.org/default.aspx?tabid=19587>
- O’Connell TJ, Bou-Matar CB. Long term marijuana users seeking medical cannabis in California (2001–2007): demographics, social characteristics, patterns of cannabis and other drug use of 4117 applicants. *Harm Reduction Journal*. 2007; 4:16. [PubMed: 17980043]
- Pacula RL, Kilmer B, Grossman M, Chaloupka FJ. Risks and prices: The role of user sanctions in marijuana markets. *The BE Journal of Economic Analysis & Policy*. 2010; 10(1)
- Pertwee RG. Cannabinoid pharmacology: the first 66 years. *Br J Pharmacol*. 2006; 147(Suppl 1):S163–171. [PubMed: 16402100]
- Prentiss D, Power R, Balmes G, Tzuang G, Israelski DM. Patterns of marijuana use among patients with HIV/AIDS followed in a public health care setting. *J Acquir Immune Defic Syndr*. 2004; 35(1):38–45. [PubMed: 14707790]
- Reiman A. Medical marijuana patients: profiles and health care utilization patterns. *Complementary Health Practice Review*. 2007; 12:31–50.
- Reiman A. Cannabis as a substitute for alcohol and other drugs. *Harm Reduction Journal*. 2009; 6(35)
- Sidney S. Marijuana use in HIV-positive and AIDS patients. Results of an anonymous mail survey. *Journal of Cannabis Therapeutics*. 2001; 1(3&4):35–41.
- Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. *The Journal of Pain*. 2008; 9(2):164–173. [PubMed: 17974490]

- Substance Abuse and Mental Health Services Administration. Results from the 2006 National Survey on Drug Use and Health: National findings (No. NSDUH Series H-32, DHHS Publication No. SMA 07-4293). Rockville, MD: Substance Abuse and Mental Health Services Administration, Office of Applied Studies; 2007.
- Wallace M, Schulteis G, Atkinson JH, Wolfson T, Lazzaretto D, Bentley H, et al. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. *Anesthesiology*. 2007; 107(5):785–796. [PubMed: 18073554]
- Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. *Anesthesia & Analgesia*. 2010; 110(2):604–610. [PubMed: 20007734]
- Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *The Journal of Pain*. 2008; 9(6):506–521. [PubMed: 18403272]
- Zuardi AW. History of cannabis as a medicine: a review. *Revista Brasileira de Psiquiatria*. 2006; 28(2):153–157. [PubMed: 16810401]

Table 1

Characteristics of applicants seeking physician recommendations for medical marijuana

	All	Females	Males	P-value
	N=1655	N=452	N=1203	
Male	72.7%	--	--	--
White	58.5%	60.0%	58.0%	0.477
Hispanic	14.5%	13.1%	15.0%	0.305
Black	10.9%	14.2%	9.7%	0.010
Native American/Asian	6.9%	5.3%	7.6%	0.108
Mixed race or other	8.9%	8.0%	9.3%	0.393
12–18 years old	0.2%	0.0%	0.2%	0.288
18–24 years old	17.8%	12.6%	19.8%	0.001
25–34 years old	27.9%	26.8%	28.3%	0.546
35–44 years old	21.8%	19.9%	22.5%	0.251
45–54 years old	19.3%	26.1%	16.8%	0.000
55+ years old	13.0%	14.6%	12.4%	0.232
Not a high school grad*	8.8%	8.6%	8.9%	0.866
High school graduate*	42.5%	35.7%	45.1%	0.001
Some college*	27.1%	31.0%	25.6%	0.031
College graduate*	21.6%	24.7%	20.4%	0.064
Employed	68.7%	60.4%	71.8%	0.000
Disabled	15.5%	19.5%	14%	0.006
Previous military service	10.5%	2.1%	13.6%	0.000
Currently insured	73.0%	78.2%	71.1%	0.004
Worker's comp	3.5%	2.9%	3.7%	0.394
MediCare	9.2%	11.9%	8.2%	0.020
MediCal	15.0%	21.7%	12.6%	0.000
Private	42.4%	41.4%	42.7%	0.619
Veterans Administration	3.2%	2.0%	3.7%	0.086

Notes: Missing employment/disability data for 3 applicants, insurance information for 13 applicants, education information for 51 applicants, and military information for 86 applicants. Education variables denote highest level obtained.

Table 2

Self report of therapeutic benefits of medical marijuana

	All	Females	Males	P-value
	N=1655	N=452	N=1203	
To relieve:				
Pain	82.6%	82.7%	82.5%	0.924
Spasms	41.3%	44.2%	40.1%	0.132
Headache	40.8%	49.3%	37.6%	<i>0.000</i>
Anxiety	38.1%	51.1%	33.3%	<i>0.000</i>
Nausea	27.7%	44.9%	21.3%	<i>0.000</i>
Depression	26.1%	35.4%	22.6%	<i>0.000</i>
Cramps	19.0%	33.4%	13.5%	<i>0.000</i>
Panic	16.9%	27.2%	13.1%	<i>0.000</i>
Diarrhea	4.8%	4.9%	4.7%	0.913
Itching	2.7%	1.1%	3.3%	<i>0.013</i>
To improve:				
Sleep	70.6%	69.0%	71.2%	0.397
Relaxation	55.6%	60.2%	53.9%	<i>0.023</i>
Appetite	38.0%	35.0%	39.2%	0.117
Focus	23.3%	19.7%	24.6%	<i>0.035</i>
Energy	15.5%	17.7%	14.7%	0.135
To prevent:				
Anger	22.7%	21.9%	22.9%	0.653
Medication side effects	22.6%	27.0%	20.9%	<i>0.009</i>
Involuntary movements	6.2%	7.3%	5.8%	0.266
Seizure	3.0%	3.8%	2.7%	0.239
As a substitute for:				
Prescription medicine	50.8%	51.1%	50.7%	0.885
Alcohol	13.2%	11.3%	13.9%	0.164

Table 3

High frequency diagnoses and diagnoses listed in Proposition 215 and SB 420

	All	Females	Males	P-value
	N=1655	N=452	N=1203	
Musculoskeletal and neuropathic chronic pain				
Low back pain	26.2%	20.4%	28.4%	<i>0.001</i>
Arthritis	18.0%	17.0%	18.4%	0.529
Lumbar degenerative disc disease	15.6%	16.6%	15.3%	0.518
Muscle spasm	11.7%	9.5%	12.5%	0.095
Cervicalgia	8.9%	11.7%	7.9%	<i>0.015</i>
Cervical degenerative disc disease	6.2%	6.2%	6.2%	0.976
Peripheral neuropathy	5.8%	8.8%	4.7%	<i>0.001</i>
Fibromyalgia	1.6%	4.0%	0.7%	<i>0.000</i>
Spasticity	0.2%	0.0%	0.2%	0.288
Any of these chronic pain ICDs	58.2%	57.3%	58.5%	0.654
Mental disorders				
Anxiety disorders	18.7%	28.5%	15.0%	<i>0.000</i>
Depression	9.3%	14.2%	7.5%	<i>0.000</i>
Bipolar disorder	2.5%	4.9%	1.7%	<i>0.000</i>
Attention deficit disorder	3.1%	2.0%	3.6%	0.100
Any of these mental disorder ICDs	22.9%	33.6%	18.9%	<i>0.000</i>
Sleep disorders				
Persistent insomnia	13.5%	13.9%	13.4%	0.769
Insomnia due to pain	8.0%	8.4%	7.9%	0.734
Any of these sleep disorder ICDs	21.3%	21.9%	21.1%	0.727
Gastrointestinal disorders				
Nausea and vomiting	7.4%	9.5%	6.6%	<i>0.041</i>
Anorexia	4.6%	4.4%	4.7%	0.842
Abdominal pain	2.9%	4.9%	2.2%	<i>0.004</i>
Gastritis and GERD	2.5%	4.0%	1.9%	<i>0.016</i>
Irritable bowel syndrome	1.1%	0.4%	1.3%	0.121
Any of these gastrointestinal disorder ICDs	13.3%	16.6%	12.1%	<i>0.015</i>
Neurologic disorders				
Migraine headache	9.2%	16.2%	6.7%	<i>0.000</i>
Other headache	6.5%	6.6%	6.5%	0.910
Seizure	1.4%	1.5%	1.3%	0.735
Multiple sclerosis	0.6%	1.1%	0.4%	0.106
Any of these neurologic disorder ICDs	16.6%	24.8%	13.5%	<i>0.000</i>
Gynecologic disorders				
Dysmenorrhea		7.7%		

	All	Females	Males	P-value
	N=1655	N=452	N=1203	
Endometriosis		1.8%		
Any of these gynecologic disorder ICDs		9.3%		
Other				
HIV/AIDS	1.6%	0.9%	1.9%	0.142
Cancer	1.5%	2.4%	1.1%	<i>0.040</i>
Glaucoma	1.3%	1.1%	1.3%	0.717

Note: Does not include all ICD9s, and excludes those that were written in.

Table 4

Previous treatments and physician's recommendations for additional treatment

	All	Females	Males	P-value
	N=1655	N=452	N=1203	
Other treatment modalities applicants tried for medical conditions				
Current prescription medication	47.6%	57.1%	44.2%	<i>0.000</i>
1–2 prescriptions	36.7%	36.1%	37.0%	0.727
3–5 prescriptions	4.4%	9.1%	2.7%	<i>0.000</i>
6+ prescriptions	6.5%	11.9%	4.5%	<i>0.000</i>
Previous prescription medication	79.5%	86.5%	76.8%	<i>0.000</i>
Past or current RX for opioids for pain	48.0%	52.3%	46.4%	<i>0.040</i>
Physical therapy	48.6%	54.4%	46.5%	<i>0.004</i>
Chiropractic	37.2%	42.3%	35.2%	<i>0.009</i>
Surgery	21.9%	22.3%	21.8%	0.804
Psychological counseling	20.7%	33.4%	16.0%	<i>0.000</i>
Acupuncture	19.6%	26.8%	16.9%	<i>0.000</i>
Therapeutic injection	15.0%	21.5%	12.6%	<i>0.000</i>
Other types of treatment	8.6%	11.1%	7.7%	<i>0.032</i>
Referrals for further evaluation and treatment				
Primary care provider	22.4%	22.6%	22.3%	0.900
Medical specialist	16.2%	16.2%	16.2%	0.977
Physical therapy	8.2%	7.1%	8.6%	0.327
Chiropractor	6.5%	3.8%	7.5%	<i>0.006</i>
Psychological counseling	5.6%	7.1%	5.0%	<i>0.098</i>
Acupuncture	1.8%	2.2%	1.6%	0.382
Homeopathy	0.2%	0.2%	0.2%	0.815
Biofeedback	0.1%	0.0%	0.1%	0.540

Use and effects of cannabinoids in military veterans with posttraumatic stress disorder

KEVIN BETTHAUSER, JEFFREY PILZ, AND LAURA E. VOLLMER

Cannabis and its synthetic derivatives are commonly used around the world to treat a variety of disease states.¹ However, controversy continues to surround cannabis and cannabinoid use as a primary or adjunctive therapy in the treatment of stress disorders. Conflicting results of published studies further blur the distinction between cannabis as a potentially beneficial alternative to conventional pharmacotherapy and behavioral therapies and cannabis as a substance that might worsen patient outcomes when used for self-medication.²⁻⁵ This article reviews published evidence regarding the use of cannabis to address symptoms of posttraumatic stress disorder (PTSD) among military veterans.

PTSD prevalence and pathophysiology

Prevalence. PTSD is defined as chronic activation of the stress response as a result of experiencing a traumatic event.^{6,7} It has been estimated that 60% of male and 50% of female persons will experience at least one traumatic experience in their lifetime, with a high rate of

Purpose. Published evidence regarding the use of cannabis and cannabis derivatives by military veterans with posttraumatic stress disorder (PTSD) is reviewed.

Summary. When inhaled or delivered orally or transdermally, cannabinoids (the psychoactive components of unrefined marijuana and various derivative products) activate endogenous cannabinoid receptors, modulating neurotransmitter release and producing a wide range of central nervous system effects, including increased pleasure and alteration of memory processes. Those effects provide a pharmacologic rationale for the use of cannabinoids to manage the three core PTSD symptom clusters: reexperiencing, avoidance and numbing, and hyperarousal. A literature search identified 11 articles pertaining to cannabis use by military veterans who met standard diagnostic criteria for PTSD. Cross-sectional studies have found a direct correlation between more severe PTSD symptomatology and increased motiva-

tion to use cannabis for coping purposes, especially among patients with difficulties in emotional regulation or stress tolerance. Data from 4 small studies suggested that cannabinoid use was associated with global improvements in PTSD symptoms or amelioration of specific PTSD symptoms such as insomnia and nightmares. Large well-designed controlled trials are needed in order to better delineate the potential role of cannabinoids as an adjunct or alternative to conventional approaches to PTSD management.

Conclusion. While further research into cannabinoid treatment effects on PTSD symptoms is required, the evaluated evidence indicates that substantial numbers of military veterans with PTSD use cannabis or derivative products to control PTSD symptoms, with some patients reporting benefits in terms of reduced anxiety and insomnia and improved coping ability.

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stress disorders in men caused by traumatic experiences associated with combat.⁸ In the United States, PTSD is diagnosed in approximately 5.2 million people annually, and these people suffer a wide range

of symptoms. Individuals serving combat tours in the line of military service are particularly vulnerable to PTSD. According to the Department of Veterans Affairs (VA), 11–20% of veterans of Operations Iraqi Free-

KEVIN BETTHAUSER, PHARM.D., is Postgraduate Year 1 (PGY1) Pharmacy Resident, Barnes-Jewish Hospital, St. Louis, MO. JEFFREY PILZ, PHARM.D., is PGY1 and 2–Master of Science in Health-System Pharmacy Administration Resident, University of Kansas Hospital, Kansas City, KS. LAURA E. VOLLMER, PHARM.D., is PGY1 Pharmacy Resident, University of Minnesota Medical Center, Minneapolis. At the time of writing, all authors were Pharm.D. students, College of Pharmacy and Health Sciences, Drake University, Des Moines, IA.

Address correspondence to Dr. Vollmer (laura.vollmer@drake.edu).

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The Clinical Consultation section features articles that provide brief advice on how to handle specific drug therapy problems. All articles are based on a systematic review of the literature. The assistance of ASHP's Section of Clinical Specialists and Scientists in soliciting Clinical Consultation submissions is acknowledged. Unsolicited submissions are also welcome.

dom and Enduring Freedom, 10% of veterans of the Persian Gulf War, and 30% of those serving during the Vietnam War have had PTSD symptoms to varying degrees.

Furthermore, patients with PTSD are at risk for other psychological disorders, including but not limited to generalized anxiety disorder, major depressive disorder, and substance use disorder, and for physical problems such as chronic pain, hypertension, and asthma.⁶

Diagnosis. PTSD symptoms are often grouped into three subgroups defined by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, criteria and often assessed in veterans using the PTSD Checklist—Military Version (PCL-M): reexperiencing (also termed intrusion), avoidance and numbing, and hyperarousal.^{9,10} Reexperiencing refers to the cluster of PTSD symptoms associated with flashbacks and vividly reliving the traumatic experience. Avoidance–numbing symptoms are those that involve the patient trying to avoid emotional feelings; such behavior disrupts personal relationships. Finally, hyperarousal symptoms include irritability, difficulty concentrating, increased worrying about safety, and reduced tolerance to startling stimuli.¹⁰ PTSD diagnosis is based on patients experiencing these symptoms for at least one month to a degree that interferes with activities of daily living or reduces quality of life.

Pathophysiology. The pathophysiology of these symptoms, while not fully understood, is thought to

be related to increased sympathetic nervous system activity due to a traumatic experience compounded by changes in memory processing. Physical manifestations of PTSD are linked to increased levels of norepinephrine but also activity at α_2 -adrenergic receptors, which counteractively impede the release of neurotransmitters from adrenergic presynaptic neurons.⁶ Alteration in memory processing is hypothesized by several sources to be the cause of psychological reliving and continued response to triggering stimuli.^{6,10,11} Involved in central processing of fear and anxiety processes as well as sympathomimetic stimulation, the amygdala and hypothalamic structures are thought to be key components of PTSD symptomatology, although their roles are not fully understood.^{10,12}

The changes in memory function associated with PTSD differ from those seen in other forms of stress.¹³ The significant difference is the lack of increased cortisol levels in persons with PTSD. One group of researchers hypothesized that the changes in neural functioning seen in patients with PTSD reduce the ability to remove traumatic memories and the remembered response to those stimuli.¹¹

Cannabinoid pharmacology

Endogenous cannabinoid ligands, or endocannabinoids, exist naturally in the body to stimulate activity at cannabinoid receptors. Drugs delivering cannabinoid compounds also activate these receptors. Specifically, cannabinoid-1 (CB-1) and cannabinoid-2 (CB-2) G-coupled protein receptors are activated by cannabis compounds, leading to the production of secondary messengers that modulate the release of neurotransmitters from presynaptic sites through both excitatory and inhibitory actions.¹⁴ CB-1 receptors are diffusely distributed within the central nervous system, which helps to explain the wide range of effects seen

with cannabinoid receptor activation; CB-1 receptors are the primary target for modification of PTSD symptoms. With cannabinoid use, pleasure is increased, while memory and concentration can be inhibited, due to the release of acetylcholine, norepinephrine, dopamine, serotonin, and glutamate neurotransmitters. CB-2 receptors are concentrated in the peripheral nervous system and elicit immunosuppressive and antiinflammatory responses when activated. Cannabinoids are highly lipophilic compounds that rapidly cross lipid membranes and the blood-brain barrier, leading to a fast onset of effect, especially when cannabinoids are inhaled. In murine models, it was demonstrated that correcting a deficiency of endogenous cannabinoids enabled mice subjected to traumatic shock treatments to overcome their conditioned response by allowing removal of the harmful stress-inducing memories through inhibition of γ -aminobutyric acid pathways in the amygdala. This mechanism is thought to explain human responses to cannabinoids as well.

Cannabinoid classification and legal status

Perhaps the most known connotation of the term *cannabinoid* to the layperson pertains to marijuana, which can deliver cannabinoids via respiratory, transdermal, and oral routes. Formally, marijuana refers to the unrefined leaves and flowers of *Cannabis sativa*, which contain over 460 active substances and no fewer than 60 cannabinoids.¹⁴ Delta-9-tetrahydrocannabinol (δ -9-THC) is the cannabinoid responsible for the majority of effects seen with marijuana use. The active compounds in marijuana produce the same activity in the messenger systems linked to cannabinoid receptors as that produced by endocannabinoids.

Cannabinoid-containing substances differ in terms of route of administration and active chemical

ingredients. Marijuana and select synthetic cannabinoids are classified by the Drug Enforcement Administration as Schedule I drugs under the Controlled Substances Act of 1970.¹⁵ This is largely due to the effects of δ -9-THC, which causes a “high” sensation and impaired cognition when inhaled or absorbed via the gastrointestinal tract. However, cannabinoids synthesized for specific disease therapies or available in other dosage forms, such as a hard-shell capsule, may be subject to other legal classifications. As of January 2014, 19 states and the District of Columbia allowed medicinal use of cannabis in select patients with certain disease states, most commonly seizure disorders and chronic pain.¹⁴

The addiction potential and stigma of marijuana use are important considerations, and the benefits of cannabinoid therapies for PTSD must be weighed against the associated adverse drug events (some of which can be life-threatening).¹⁴ The purpose of this review is to analyze current relevant literature surrounding the use of cannabis and cannabinoids for PTSD symptom control by military veterans, with the goal of providing insights on whether these treatments improve or worsen patient outcomes.

Methods and results of literature review

During the period February 10–October 1, 2014, a comprehensive literature search covering the period January 1, 1995, to October 1, 2014, was conducted using PubMed (MEDLINE) and Academic Search Complete (EBSCO Industries, Inc., Ipswich, MA). Both Medical Subject Headings (MeSH) terms and the subheadings feature of PubMed were used. Keywords were searched separately in combination with appropriate Boolean operators.

Keywords in searches included *PTSD*, *post traumatic stress disorder*, *medical marijuana*, *cannabis*, *medical cannabis*, *marijuana*, and *combat vet-*

erans (appendix). For the purposes of this review, the term *cannabinoid* was considered to apply to endocannabinoids. On identification of articles that met the inclusion criteria, the references cited therein were analyzed for additional relevant articles not identified in the original keyword and MeSH term searches.

The article/study inclusion criteria that were applied to each item retrieved in the search were as follows:

- Reported outcome(s) related to the general use of cannabinoids among persons with a diagnosis of PTSD associated with military experience or the use of cannabinoids for the amelioration of PTSD symptoms associated with military experience
- Pertained to research in humans
- Was written in the English language
- Pertained to individuals with PTSD diagnosed via a standard scale (e.g., *DSM-IV* or *DSM-5* criteria, Impact of Event Scale—Revised)

Editorials and opinion pieces were excluded from the review.

Each article identified for inclusion in the review was analyzed by the authors individually and collaboratively in order to determine its clinical relevance and relative standing in the realm of data supporting or militating against medicinal cannabis use for PTSD symptoms.

A total of 59 articles were identified through PubMed and the EBSCO database. Pursuant to application of the inclusion and exclusion criteria, 11 articles were included in this review. A variety of study designs were represented in the list of selected articles, and all evaluated research supported two general concepts: (1) many people suffering from PTSD use cannabis for symptom alleviation, and (2) some people find it of benefit in that regard.

Cannabinoids and coping mechanisms

Several studies supported the

relationship between cannabinoid use and coping behavior, with usage tending to increase with PTSD symptom severity.^{2,5,16-18} Bonn-Miller et al.¹⁶ conducted a cross-sectional study that examined the relationship between PTSD symptom severity and motives for marijuana use among 103 young adult marijuana users who reported at least one traumatic event in their lifetime. The study concluded that symptom severity was significantly related to coping-oriented marijuana use motives. Furthermore, levels of post-traumatic stress were not related to other motives for marijuana use, providing evidence of “discriminant validity” (a construct aimed at showing that things that should not be related are, in fact, not related) and empirical evidence of coping motives for marijuana use.

In other research, Bonn-Miller and colleagues⁵ used a cross-sectional study design to examine the correlation between difficulty in emotional regulation and use of cannabis as a coping mechanism in patients who have experienced traumatic life events. The study surveyed a fairly homogeneous sample of adults who reported marijuana use within the previous 30 days. A multitude of surveys were used to determine marijuana use, the presence of PTSD symptoms, and each participant’s level of difficulty with emotional regulation. The investigators found that PTSD symptom severity and difficulty in emotional regulation were both significantly predictive of coping-oriented marijuana use. Furthermore, PTSD symptom severity predicted the degree of difficulty in emotional regulation even when the frequency of marijuana use was controlled.

Bonn-Miller et al.¹⁷ subsequently hypothesized that patients with PTSD using medical marijuana for sleep might increase their use in an attempt to cope with more severe symptoms. As in their previous research, the investigators chose a

cross-sectional study design, evaluating coping-use motivations, cannabis and alcohol use, and other outcomes in a convenience sample of male and female adult patients buying cannabis from a licensed dispensary. Based on PCL-M scores, two groups were formed: patients without PTSD (defined as a PCL-M score of ≤ 30 [$n = 95$]) and patients with PTSD (defined as a score of >30 [$n = 75$]). The study results showed that patients with PTSD had a greater motivation to use cannabis for sleep and coping reasons than the non-PTSD group regardless of comorbid alcoholism or depressive symptoms. This study was limited by its narrow focus on patients who were already using medical marijuana. As the researchers noted, the fact that tolerance to marijuana's sleep-inducing effects can develop seemed inconsistent with the finding that PTSD led to increased use of cannabis.

Potter et al.¹⁸ conducted a cross-sectional study ($n = 142$) of adults in Vermont with PTSD to investigate the role of distress tolerance in relation to PTSD symptom severity and marijuana use. The researchers found that PTSD symptom severity was positively correlated with marijuana-use coping motives ($r = 0.37, p < 0.01$) and negatively correlated with distress tolerance ($r = -0.47, p < 0.01$). Their overall conclusion was that distress tolerance may play a partial role in mediating the relationship between PTSD symptom severity and coping-oriented marijuana use.

Cannabinoids, worsening of PTSD symptoms, and substance abuse

Studies included in this review examined the possible link between cannabis use and worsening of PTSD symptoms or concomitant substance abuse.^{2,19} Bonn-Miller et al.² used a prospective cohort study design to analyze cannabis use in relation to PTSD symptom severity in a population of 432 male military veterans (mean \pm S.D. age, 51 ± 4

years) admitted to a VA residential treatment program for patients with PTSD. Cannabis use four months after the completion of the rehabilitation program was significantly more likely in program participants with lower levels of improvement from intake to discharge in PCL-M scores for avoidance–numbing and hyperarousal symptom clusters ($p < 0.05$). The researchers concluded that lower improvement in PCL-M scores at program completion was significantly predictive of an increased risk of cannabis use within the four months after discharge.

Although this study lacked generalizability (i.e., it involved only patients seen in a VA residential rehabilitation program), it suggested that specific symptoms have more influence than others on PTSD patients' desire to use cannabis. A major limitation of this study was that patients in the rehabilitation program were required to quit marijuana use for the duration of their treatment, but the effect of cannabinoid withdrawal was not included in the analysis. Furthermore, the study involved a nonrandomized sample, raising the possibilities of high subjectivity and bias.

Bremner et al.¹⁹ conducted a similar cross-sectional study of Vietnam War military veterans ($n = 61$) in the northeastern United States. This study aimed to measure the progression of some PTSD symptoms and related alcohol and substance abuse symptoms, as well as the effects of abused substances on those PTSD symptoms. The researchers found that PTSD symptoms were increased among veterans using substances such as alcohol, heroin, cocaine, and marijuana. Further, the study showed that veterans using said substances reported benefits with regard to PTSD symptoms.

Cannabinoids and reduction of PTSD symptoms

Research also has examined the reduction of PTSD symptom sever-

ity after treatment with cannabis products.^{3,4} A study by Mashiah⁴ examined the use of medical cannabis in Israeli military veterans ($n = 29$) with diagnosed chronic PTSD. Study participants were given no more than 100 g of cannabis per month and instructed to smoke the cannabis daily at frequencies and amounts of their own choosing. Patients were reassessed three times throughout one year by their psychiatrists. At each reassessment, the study found that the average total Clinician-Administered PTSD Scale (CAPS) score was reduced relative to previously assessed and baseline scores. However, all patients still met the criteria for moderate-to-severe PTSD. This report did not describe the baseline cannabis-use characteristics of the evaluated patients. Additionally, only 10 participants were reassessed after the second follow-up, with no explanation provided by the study author.

Greer et al.³ performed a chart review–based study of 80 patients with PTSD participating in New Mexico's Medical Cannabis Program. The total CAPS score and CAPS symptom-cluster scores for reexperiencing, avoidance–numbing, and hyperarousal symptoms were significantly reduced ($p < 0.0001$) when patients were using cannabis relative to scores obtained under the no-cannabis condition. Overall, patients reported more than 75% reductions in all three areas of PTSD symptoms while using cannabis. It should be noted that participants in this study had already found cannabis to reduce their PTSD symptoms and, partly for that reason, sought entry into the cannabis program (they also sought to avoid criminal penalties for marijuana possession); as a result, they might have been predisposed to report reduced symptoms. Further, it is possible that subjects exaggerated their PTSD symptoms during initial CAPS assessment in hopes of qualifying for the program. While this study

sheds some light on the possibility of medical cannabis being an effective treatment for PTSD, it lacked a control sample of PTSD sufferers with no prior experience with cannabis and involved a large potential and motives for bias.

Nabilone, a synthetic endocannabinoid receptor agonist, has been studied for potential usefulness in mitigating PTSD symptoms, particularly insomnia and nightmares.^{20,21} Cameron et al.²⁰ conducted a retrospective chart review–based study of patients with mental illness ($n = 104$) who received nabilone while admitted to a correctional and treatment facility in Canada (90% of the patients had PTSD). The researchers looked at indications for nabilone use, effectiveness and safety outcomes, and medications discontinued when cannabinoids were added to patients' regimens. Nabilone was used to treat a mean of 3.5 indications per patient, most commonly nightmares, insomnia, and chronic pain. Improvement in PTSD symptoms was assessed via analysis of scores on the PTSD Checklist—Civilian (PCL-C), which is very similar to the PCL-M, and the Global Assessment of Functioning (GAF). On average, posttreatment PCL-C scores were significantly decreased ($p = 0.001$) from pretreatment scores, allowing many cases initially classified as moderate-severity PTSD to be reclassified as borderline or mild cases; the mean GAF score increased significantly ($p = 0.001$), indicating improved functioning and decreased symptoms. Thirty-one patients reported adverse events during treatment with nabilone, the most serious being psychosis; of those 31 patients, 10 chose to abandon the study. The authors concluded that nabilone can potentially decrease PTSD symptoms, including insomnia and nightmares, in patients with diagnosed cannabis dependence.

Another investigator conducted an open-label clinical trial to

evaluate the effects of nabilone on treatment-resistant nightmares in patients ($n = 47$) with PTSD.²¹ Patients were reviewed after adjunctive treatment with 0.5 mg of nabilone one hour before bedtime. Thirty-four patients (72%) receiving nabilone experienced either cessation of nightmares or a significant reduction in nightmare intensity. The researcher also found subjective improvements in terms of sleep time and daytime flashbacks. The results of the study indicated the potential benefits of nabilone in patients with PTSD experiencing poor control of nightmares with standard pharmacotherapy.

Discussion

All articles evaluated in this review indicated that individuals suffering from PTSD symptoms related to military experiences often use cannabis or cannabinoids as a means of coping, with some reporting benefits. The studies also suggested that the pathogenesis of PTSD—and, most likely, effective treatment—is multifactorial.

Of note, the research described in the reviewed articles was generally limited by the use of small nonrandomized and/or self-selected samples that lacked control groups and carried a high potential for recall bias and type II error. These limitations should be the catalyst for further research through large, randomized, placebo-controlled trials. With growing evidence that patients with PTSD use cannabis and its derivatives as a means of symptom alleviation, it is becoming necessary for the healthcare community to better understand this phenomenon.

There is a growing need for research comparing the effects of cannabinoids with those of conventional pharmacotherapies currently used in PTSD (e.g., prazosin, selective serotonin reuptake inhibitors, second-generation antipsychotics) and cognitive-behavioral therapy. Head-to-head comparisons of the

conventional therapies with cannabinoids are needed in order to demonstrate whether one treatment is superior to another in terms of safety or efficacy. Like cannabinoids, all current pharmacotherapies used for PTSD carry known risks that potentially outweigh benefits from use. With the rising number of veterans returning from recent conflict zones, and a subsequent rise in PTSD cases, the need for quality research in this area is great.

Conclusion

While further research into cannabinoid treatment effects on PTSD symptoms is required, the evaluated evidence indicates that substantial numbers of military veterans with PTSD use cannabis or derivative products to control PTSD symptoms, with some patients reporting benefits in terms of reduced anxiety and insomnia and improved coping ability.

References

1. O'Brien CP. Drug addiction. In: Brunton L, ed. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill; 2011:663-4.
2. Bonn-Miller MO, Vujanovic AA, Drescher KD. Cannabis use among military veterans after residential treatment for post-traumatic stress disorder. *Psychol Addict Behav*. 2011; 25:485-91.
3. Greer GR, Grob CS, Halberstadt AL. PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program. *J Psychoactive Drugs*. 2014; 46:73-7.
4. Mashiah M. Medical cannabis as treatment for chronic combat PTSD: promising results in an open pilot study. Presentation at Patients Out of Time Conference, Tucson, AZ; 2012 Apr 28.
5. Bonn-Miller MO, Vujanovic AA, Boden MT et al. Post-traumatic stress, difficulties in emotion regulation, and coping-oriented marijuana use. *Cogn Behav Ther*. 2011; 40:34-44.
6. Yehuda R. Post-traumatic stress disorder. *N Engl J Med*. 2002; 346:108-14.
7. Galea S, Nandi A, Viahov D. The epidemiology of post-traumatic stress disorder after disasters. *Epidemiol Rev*. 2005; 27:78-91.
8. Department of Veterans Affairs National Center for PTSD. How common is PTSD? Frequently asked questions. www.ptsd.va.gov/public/PTSD-overview/basics/

- how-common-is-ptsd.asp (accessed 2013 Feb 20).
9. Bonn-Miller MO, Boden MT, Vujanovic AA. Prospective investigation of the impact of cannabis use disorders on post-traumatic stress disorder symptoms among veterans in residential treatment. *Psychol Trauma*. 2013; 5:193-200.
 10. Porth CM. *Essentials of pathophysiology*. 3rd ed. Philadelphia: Wolters Kluwer Health; 2011:219-22.
 11. Marsicano G, Wotjak CT, Azad CA et al. The endogenous cannabinoid system controls extinction of aversive memories. *Nature*. 2002; 418:530-4.
 12. Trezza V, Campolongo P. The endocannabinoid system as a possible target to treat both the cognitive and emotional features of post-traumatic stress disorder (PTSD). *Front Behav Neurosci*. 2013; 7:1-6.
 13. Yehuda R. Biology of post-traumatic stress disorder. *J Clin Psychiatry*. 2000; 61:14-21.
 14. Seamon MJ, Fass JA, Maniscalco-Feichtl M et al. Medical marijuana and the developing role of the pharmacist. *Am J Health-Syst Pharm*. 2007; 64:1037-44.
 15. Abood RR. *Pharmacy practice and the law*. 7th ed. Burlington, MA: Jones and Bartlett Learning; 2014:184-216.
 16. Bonn-Miller MO, Vujanovic AA, Feldner MT et al. Post-traumatic stress symptom severity predicts marijuana use coping motives among traumatic event-exposed marijuana users. *J Trauma Stress*. 2007; 20:577-86.
 17. Bonn-Miller MO, Babson KA, Vandrey R. Using cannabis to help you sleep: heightened frequency of medical cannabis use among those with PTSD. *Drug Alcohol Depend*. 2014; 136:162-5.
 18. Pottter CM, Vujanovic AA, Marshall-Berenz EC et al. Post-traumatic stress and marijuana use coping motives: the mediating role of distress tolerance. *J Anxiety Disord*. 2011; 25:437-43.
 19. Bremner JD, Southwick SM, Darnell A et al. Chronic PTSD in Vietnam combat veterans: course of illness and substance abuse. *Am J Psychiatry*. 1996; 153:369-75.
 20. Cameron C, Watson D, Robinson J. Use of a synthetic cannabinoid in a correctional population for posttraumatic stress disorder-related insomnia and nightmares, chronic pain, harm reduction, and indications: a retrospective evaluation. *J Clin Psychopharmacol*. 2014; 34:559-64.
 21. Fraser G. The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in post-traumatic stress disorder (PTSD). *J CNS Neurosci Ther*. 2009; 15:84-8.

Appendix—Keyword strings used in literature search

(medical marijuana OR medical cannabis OR marijuana OR cannabis) AND PTSD
 medical marijuana AND PTSD
 medical cannabis AND PTSD
 marijuana AND PTSD
 cannabis AND PTSD
 medical marijuana AND PTSD NOT depression
 medical marijuana AND combat veterans
 medical cannabis AND combat veterans
 marijuana AND combat veterans
 cannabis AND combat veterans

THE USE OF INDIAN HEMP IN THE TREATMENT OF CHRONIC CHLORAL AND CHRONIC OPIUM POISONING.

BY EDWARD A. BIRCH, M.D., M.R.C.P.,

HONORARY MEMBER OF THE CALCUTTA MEDICAL SOCIETY; PHYSICIAN TO THE GENERAL HOSPITAL, CALCUTTA.

IN 1887, at Calcutta, at nearly the same time, I met with two cases, both of them distressing and interesting. The first was that of a European gentleman, who I remembered to have met some two years previously, when he brought his wife from a distant district with a view to placing her under a physician in consequence of her habits as a confirmed chloral drinker. At that time I discovered that she was also a sufferer from valvular cardiac disease; but I need allude no further to her than to state that no power of persuasion or fear of consequences produced any effect. She made no real effort to overcome her vice. When denied her regular dose on two occasions, she became so outrageous, and, in her husband's opinion, so alarmingly ill, that she remained but a few days in town. Her husband then stated that his wife had continued her habit, and that she ultimately died. The object of his visit was, he stated, to consult me about his heart. A very careful examination of that organ enabled me to assure him that it was healthy, though it certainly was in an irritable condition. Thus encouraged, he went on, to my amazement, to tell me that he had followed in his wife's footsteps, that he could not live without chloral, that he was utterly miserable, and that he took about forty grains daily. His depression of spirits he described as being terrible; he had frequently contemplated suicide; insomnia was almost complete, no sleep whatever being obtained without the aid of chloral, and then but little. He could take scarcely any food. The patient was a fresh, healthy-looking man, whose occupation was out-door and health-giving. He neither drank nor smoked. Change of air and scene had proved useless, but then he had never been able to release himself from his habit. I could not ascertain, with any certainty, how long he had been addicted to chloral, but I suspected he commenced it long before his wife's death, though that event was the excuse he offered in extenuation. His organs were healthy, and worked healthily, except the functionally deranged heart. I prescribed a sea trip, a mixture containing tinct. cannabis indica (ten minims), tinct. strophanth., and tinct. chlorof. co., with a bitter infusion, and appealed to him in the strongest language to abandon his vice. Six weeks later he returned, in much the same state, and reported that at first he had improved, but soon became intermittent in the use of his medicine, and he had not given up his chloral. He now agreed voluntarily to place himself under circumstances which admitted of surveillance and restraint. His chloral was peremptorily stopped, and he was prescribed a pill containing half a grain of ext. cannabis ind. with a few grains of the compound colocynth pill, to be taken three times a day. The result was an *immediate* improvement. The craving for the chloral had almost vanished in twenty-four hours, natural sleep returned after a few days, and he began to enjoy his food. Eventually he returned to his home and work, a happy man; but much disappointed because the name of the drug used was not communicated to him.

The second case was briefly this: I was requested by his friends to see a young Eurasian gentleman, whom I found to be a most miserable object, aged about twenty-four years, yellow, intensely anæmic, and extremely emaciated—an "exhumed corpse," in fact, lying upon a couch, suffering acute agony in every limb. His liver and spleen were both materially enlarged. His history was shortly this. Occupying a position of considerable responsibility, and compelled to reside in one of the most desolate and depressing regions of Bengal, he became a confirmed and very excessive spirit drinker, till, fearing the consequences, he resolved to conquer the habit, and he did so most thoroughly, but with the frightful assistance of opium. Laudanum was the form selected, and for at all events four months prior to his coming under my notice he admitted having consumed not less than two ounces daily. His friends, who had only just rescued him from his isolated position, were quite hopeless

of the possibility of recovery. Here there was the well-known train of symptoms—insomnia, anorexia, disordered bowels, conscious delusions, though there was no confusion of ideas in conversation, and so forth. Again I resorted to cannabis, commencing with only a quarter of a grain of the extract, gradually increasing it to half a grain, one grain, and one grain and a half three times a day, with the happiest result. Ability to take food and retain it soon returned, and after a time an appetite appeared; he began to sleep well; his pulse, which could not be counted at first, exhibited some volume; flesh rapidly accumulated; and after three weeks he was able to take a turn upon the verandah with the aid of a stick. After the lapse of six weeks he spoke of returning to his post, and I never saw him again.

I have never before or since had such typical cases of this class to deal with, but I have lost no opportunity of testing the cannabis in the direction indicated as far as possible, and I am satisfied of its immense value. The chief point that struck me was the *immediate* action of the drug in appeasing the appetite for the chloral or opium, and in restoring the ability to appreciate food. It seems to supply the place of the poison, to stimulate the appetite, to increase the heart's power, and thus to procure sleep indirectly, as well as directly, by its own sedative effect. Moreover, I am convinced that it is a diuretic, and that this action helped in the above cases. I prescribed the cannabis simply with a view to utilising a well-known remedy for insomnia, but it did much more than procure sleep. I think it will be found that there need be no fear of peremptorily withdrawing the deleterious drug, if hemp be employed. I know that the mere withdrawal of chloral will effect a cure, but at the expense of an interval of suffering which need not be incurred; and the same in a different degree holds true of opium. Upon one point I would insist—the necessity of concealing the name of the remedial drug from the patient, lest in his endeavour to escape from one form of vice he should fall into another, which can be indulged with facility in any Indian bazaar in the forms of gunjah (the dried flowering tops), churrus (the resinous exudation), bang or subzee (the larger leaves and capsules), or majoon (a compound of bang, butter, and flour). Hence the prescription should be made as complex as possible, and at the earliest moment the dose of the extract should be diminished gradually till eventually it is withdrawn altogether from the prescription.

Calcutta.

A SUCCESSFUL CASE OF PROCTOTOMY FOR MALIGNANT DISEASE.

BY C. STONHAM, F.R.C.S. ENG.,

ASSISTANT SURGEON TO THE WESTMINSTER HOSPITAL.

GEORGE B—, aged sixty-one, a platelayer, came under my care on Jan. 24th, 1887, with the following history. About a year previously he first noticed pain during defecation, with frequent loss of blood. At first he did not attach much importance to these symptoms, but they gradually became more severe and the pain was more or less constant. Latterly he had had frequent attacks of diarrhoea, accompanied by pain of a burning character. There had not been any irritability of the bladder or any difficulty in micturition. The patient had always been a spare man, weighing at this time 10st.; he did not think he had lost flesh lately. Family history good.

State on admission.—About one inch from the margin of the anus there was a hard nodulated mass extending all round the circumference of the gut, and upwards for about two inches, the finger just reaching its upper limit, but when coughing the whole growth slipped over the finger like a ring. The edge of the mass was rounded. There was no involvement of surrounding parts, the whole gut being freely movable. Examination caused considerable hæmorrhage. The patient said that he felt in perfect health, and was merely seeking relief from the constant local annoyance.

Operation.—On Jan. 29th, the patient's bowels having been previously thoroughly opened by castor oil and enemata, about fifteen ounces of warm boracic acid lotion

Cannabis for chronic pain: Case series and implications for clinicians

Mark A Ware MBBS MRCP(UK) MSc¹, Ann Gamsa PhD¹, Jan Persson MD PhD²,
Mary-Ann Fitzcharles MD FRCPC¹

MA Ware, A Gamsa, J Persson, M-A Fitzcharles. Cannabis for chronic pain: Case series and implications for clinicians. *Pain Res Manage* 2002;7(2):95-99.

BACKGROUND: Chronic pain is one of the most common reasons for therapeutic cannabis use.

OBJECTIVES: To describe therapeutic cannabis use among patients with chronic pain.

METHODS: Patients with chronic pain who voluntarily indicated that they used cannabis therapeutically completed a questionnaire about the type of cannabis used, the mode of administration, the amount used and the frequency of use, and their perception of the effectiveness of cannabis on a set of pain-associated symptoms and side effects. The study was approved by the McGill University Health Centre Research Ethics Board.

RESULTS: Fifteen patients (10 male) were interviewed (median age 49.5 years, range 24 to 68 years). All patients smoked herbal cannabis for therapeutic reasons (median duration of use six years, range two weeks to 37 years).

Seven patients only smoked at night-time (median dose eight puffs, range two to eight puffs), and eight patients used cannabis mainly during the day (median dose three puffs, range two to

eight puffs); the median frequency of use was four times per day (range one to 16 times per day).

Twelve patients reported improvement in pain and mood, while 11 reported improvement in sleep. Eight patients reported a 'high'; six denied a 'high'. Tolerance to cannabis was not reported.

CONCLUSIONS: The results of this self-selected case series must be interpreted with caution. Small doses of smoked cannabis may improve pain, mood and sleep in some patients with chronic pain. Clinical trials are warranted to test these effects. Further prospective studies should examine the patterns and prevalence of cannabis use among chronic pain populations.

Key Words: *Analgesia; Cannabinoids; Cannabis; Pain*

Le cannabis contre la douleur chronique : Une série de cas et les répercussions pour les cliniciens

HISTORIQUE : La douleur chronique est l'une des principales causes d'utilisation du cannabis pour des raisons thérapeutiques.

OBJECTIFS : Décrire l'usage du cannabis pour des raisons thérapeutiques chez des patients souffrant de douleur chronique.

Suite à la page suivante

¹McGill University Health Centre-Montreal General Hospital Pain Centre, Montreal General Hospital, Montreal, Quebec; ²Department of Anaesthesia, Huddinge Universitetssjukhus, Stockholm, Sweden

Correspondence and reprints: Dr Mark Ware, Montreal General Hospital, Room D10.137, 1650 Cedar Avenue, Montreal, Quebec H3G 1A4.

Telephone 514-934-2222, fax 514-934-8096, e-mail mark.ware@muhc.mcgill.ca

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MÉTHODOLOGIE : Des patients souffrant de douleur chronique qui ont volontairement indiqué utiliser du cannabis pour des raisons thérapeutiques ont répondu à un questionnaire sur le type de cannabis utilisé, le mode d'administration, la quantité utilisée et la fréquence d'utilisation, ainsi que sur leur perception de l'efficacité du cannabis sur un ensemble de symptômes et d'effets secondaires associés à la douleur. L'étude a été approuvée par le conseil de recherche déontologique du Centre universitaire de santé McGill.

RÉSULTATS : Quinze patients (10 hommes) ont été interrogés (âge moyen : 49,5 ans, plage de 24 à 68 ans). Tous les patients fumaient du cannabis végétal pour des raisons thérapeutiques (durée moyenne de six ans, plage de deux semaines à 37 ans).

Sept patients ne fumaient que le soir (dose moyenne de huit bouffées, plage de deux à huit bouffées), et huit patients utilisaient le cannabis

surtout le jour (dose moyenne de trois bouffées, plage de deux à huit bouffées). La fréquence moyenne d'utilisation correspondait à quatre fois par jour (plage de une à 16 fois par jour).

Douze patients ont fait état d'une diminution de leur douleur et d'une amélioration de leur humeur, tandis que 11 ont déclaré mieux dormir. Huit patients ont affirmé ressentir un état d'euphorie, et six l'ont nié. Aucune tolérance au cannabis n'a été déclarée.

CONCLUSIONS : Les résultats de cette série de cas par autosélection doivent être interprétés avec prudence. De petites doses de cannabis fumé pourraient réduire la douleur et améliorer l'humeur et le sommeil chez certains patients atteints de douleur chronique. Des essais cliniques s'imposent pour vérifier ces effets. Des études prospectives supplémentaires devraient porter sur les schémas et la prévalence d'utilisation de cannabis au sein des populations souffrant de maladie chronique.

The use of *Cannabis sativa* in the treatment of pain has been described in the literature since 3000 BC (1). The recent discovery of specific cannabinoid receptors (2,3) and endogenous cannabinoid ligands (4,5) that play an important role in pain transmission (6) has renewed interest in natural and synthetic cannabinoids as therapeutic agents. This recent scientific activity has occurred in parallel with rising popular support in Canada and elsewhere for the use of herbal cannabis as a medicinal agent (7). Health Canada has issued a call for research into the medicinal uses of cannabis, including the evaluation of smoked cannabis in clinical trials (8).

Dose-response considerations are among the first issues to be considered in designing a study of a new drug in humans. Currently, data on cannabis dose requirements for therapeutic effect are limited to oral preparations of delta-9-tetrahydrocannabinol (THC) and cannabis extracts. There are few data on the doses of smoked cannabis used by medicinal users, but such information may be useful in estimating starting doses for clinical trials and for developing other modes of cannabinoid drug delivery.

Chronic pain often involves a complex constellation of symptoms, including pain, anxiety, fatigue, limitation of activity and depression, all of which contribute to a reduced quality of life. Preclinical research provides compelling evidence that cannabinoids exhibit antinociceptive effects in animal models of acute pain and chronic inflammatory and neuropathic pain (9). Oral THC has been found to have some analgesic effect in cancer pain (10). Oral preparations of whole cannabis containing several cannabinoids have been found to reduce opioid requirements in a single patient trial (11). Smoked cannabis has never been studied in a clinical trial of chronic pain, but anecdotal reports of patients who have smoked cannabis for pain relief suggest that the effects are varied, and include relaxation, reduced anxiety, improved sleep and improved concentration (12). The effects of smoked cannabis on chronic pain may, therefore, be more complex than simple analgesia.

We present a case series of 15 patients with chronic pain who reported having used cannabis for symptom relief. The

objectives of the study were to determine the main reasons for using cannabis, the dose size and frequency, the desired and adverse effects, and the experience of tolerance to these effects.

PATIENTS AND METHODS

Patients were recruited from two sites – the McGill Pain Centre and a university-affiliated rheumatology clinic. The McGill Pain Centre is a tertiary referral centre for the multidisciplinary management of chronic pain. The clinic sees over 250 new patients per year and has over 1000 patients on the register. The rheumatology clinic is staffed by three academic rheumatologists and is located about 20 km from the downtown centre of Montreal. As part of the routine assessment of new patients, patients are asked about the previous use of pain management techniques, including conventional and unconventional therapies, and the degree of benefit or side effects derived from these treatments. They are not asked specifically about cannabis use. Over a six-month period from February to July 2001, 15 patients chose to report cannabis use for symptom management. These patients were invited to participate in the present study. A structured questionnaire was administered in the presence of the primary caregiver. The diagnosis was provided by the primary care giver. Cannabis use was described by the type of material used (herbal, resin, oil) and method of administration (smoked, eaten, tea). A single dose was defined as the number of puffs or joints taken at any discrete point in time, and frequency was defined as the number of such doses per day. A joint was assumed to be equivalent to eight puffs (13). Patients were asked to indicate which symptoms were present and to categorize the perceived effectiveness of cannabis on each symptom (improved, no change, worse). Because some side effects of cannabis use may be considered by patients to be desirable (eg, the 'high' associated with use), they were asked to rate the side effects qualitatively.

For statistical analysis, perceived effectiveness and side effects were handled as ordered categorical variables and assigned rank scores. Correlations between dose (single and

TABLE 1
Pain syndromes of 15 patients with experience of therapeutic cannabis use

Age (years)	Sex	Pain diagnosis
24	Male	Ankylosing spondylitis
35	Female	Multiple sclerosis
36	Male	Musculoskeletal pain
40	Male	Cervical radiculopathy
43	Male	Fibromyalgia
44	Female	Rheumatoid arthritis
46	Male	Reflex sympathetic dystrophy
48	Male	Phantom limb pain
51	Male	Fibromyalgia
51	Male	Lumbar radiculopathy
52	Male	Seronegative spondyloarthropathy
53	Female	Complex regional pain syndrome
58	Male	Lumbar radiculopathy
64	Female	Chronic pancreatitis
68	Female	Rheumatoid arthritis

total daily) and effectiveness or side effect scores were examined by one-way ANOVA using Stata version 6.0 (Stata Corporation, USA).

Approval for the study was obtained from the McGill University Health Centre Research Ethics Board, and all patients provided written informed consent.

RESULTS

Fifteen patients (10 male) – 10 from the pain centre and five from the rheumatology clinic – participated in the survey. The median age of the participants was 49.5 years (range 24 to 68 years). The chronic pain syndromes are listed in Table 1. Three patients had spinal radiculopathy (one cervical, two lumbar); two patients had rheumatoid arthritis; two patients had fibromyalgia; two patients had complex regional pain syndrome; and one patient each had phantom limb pain, ankylosing spondylitis, multiple sclerosis, chronic pancreatitis, seronegative spondyloarthropathy and a musculoskeletal pain that was not otherwise specified.

All patients smoked herbal cannabis from the flowering heads of the plant – 10 in joints, three in pipes and two in both forms. Additionally, cannabis was eaten by two patients and was taken as a tea by one. The median duration of therapeutic cannabis use was six years (range two weeks to 37 years).

Dose size and frequency exhibited wide variability, and could be divided into two main categories: night-time users, who only smoked at night (seven patients), and daytime users (eight patients), who smoked at intervals during the day and night. The median single dose for nighttime users

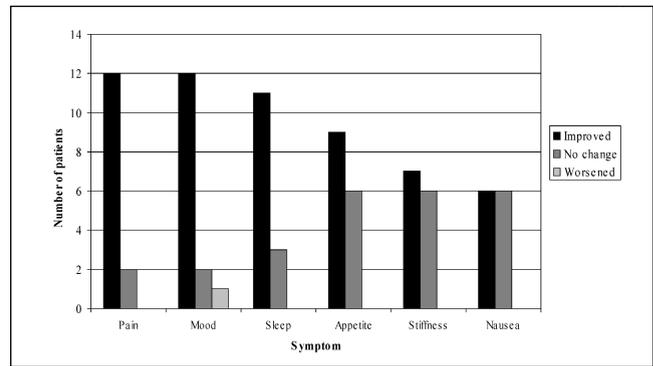


Figure 1) Perceived effectiveness of cannabis on symptoms among 15 patients with chronic pain who used cannabis

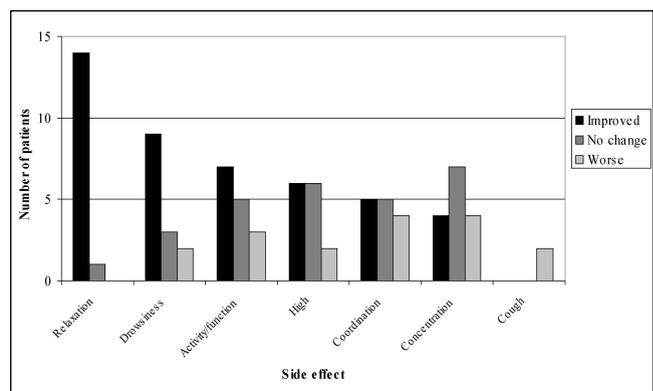


Figure 2) Perception of the side effects of smoked cannabis among 15 patients with chronic pain

was eight puffs (range two to eight puffs). The median single dose for daytime users was three puffs (range two to eight puffs), with a median frequency of four times per day (range one to 16 times per day).

The perceived effectiveness of cannabis on selected symptoms is shown in Figure 1. All 15 patients reported effects on mood (12 reported an improvement, two reported no change and one reported a worsened mood) and appetite (nine reported an improvement and six reported no change). Fourteen patients reported effects on pain (12 reported an improvement and two reported no change) and sleep (11 reported an improvement and three reported no change). Thirteen patients reported effects on stiffness (seven reported an improvement and six reported no change). Twelve patients reported effects on nausea (six reported an improvement and six reported no change).

The experience of side effects of cannabis among the 15 patients is shown in Figure 2. Fifteen patients reported effects on relaxation (14 reported an improvement and one reported no change), change in level of activity (seven reported an improvement, five reported no change and three reported a decrease) and ability to concentrate (four reported an improvement, seven reported no change and four reported a worsening). Fourteen patients reported effects on drowsiness (nine reported an improvement, three

reported no change and two reported a worsening), 'high' (six reported an improvement, six reported no change and two reported a worsening) and coordination (five reported an improvement, five reported no change and four reported a worsening). Two patients reported having a cough.

Neither single nor total daily dose was related to the perceived effectiveness of any of the symptoms. For all patients, 'high' was significantly associated with individual dose size ($F=18.49$, $P=0.001$) but not with total daily dose ($F=0.64$, $P=0.44$). After excluding daytime users, the relationship between single dose and 'high' remained significant for the nighttime users ($F=24.11$, $P=0.0044$).

DISCUSSION

This survey of 15 patients with chronic pain who reported using cannabis for therapeutic purposes is limited by its small size, inherent self-selection bias and lack of control group and should, therefore, be interpreted with considerable caution. We are cognizant of the fact that our data came mainly from those who had tried cannabis and found it tolerable and effective; only one subject in our case series reported that cannabis use was completely unhelpful and associated with debilitating side effects. Despite these limitations, we believe that our study raises some interesting points.

The first point is that pain relief is only one outcome to be addressed in trials of cannabis or cannabinoids for pain. The patients with chronic pain in this survey reported effects of cannabis on pain, sleep and mood. Some patients also reported that cannabis improved their functional status, and their ability to concentrate and relax. This finding is contrary to reported behavioural changes such as the amotivational syndrome (14) and cognitive impairment (15) in long term recreational users. This paradox has been observed in patients with chronic cancer pain whose responses to morphine in performance tasks were different from those of healthy subjects (16). Pain itself may reduce the ability to concentrate on task performance; therefore, while cannabis may impair concentration in healthy subjects, pain patients might experience a different effect. We also note that the 'high' associated with cannabis use may be perceived as a beneficial effect by patients rather than an undesirable side effect. Therefore, we recommend that, in addition to pain, a range of objective, subjective and functional outcomes including mood, quality of life and sleep should be assessed in both short term and long term studies of cannabis and cannabinoids in chronic pain states.

A second point that arises from this survey is the difficulty in estimating therapeutic dose sizes. In this series, most patients reported using herbal cannabis smoked as a joint, with doses ranging from two puffs at night to several joints per day. There are several potential sources of variability to be considered in estimating doses from such survey data. First, individual patients have different ideas of what constitutes a joint (including size, tobacco admixture and presence of a filter), and may have different puff sizes; the cannabis that they use comes from different sources,

which may independently influence the amount of cannabinoid delivered. Second, the type of cannabis preparation used must be considered in deriving dose estimates from such patient data. While cannabis potency is usually measured in terms of THC content, herbal cannabis is known to contain a mixture of other cannabinoids in addition to THC. While THC is the most abundant cannabinoid in drug-type cannabis, nonpsychoactive cannabinoids such as cannabidiol may possess anti-inflammatory, antispasticity and sedative properties that offer potential benefit in disorders such as arthritis (17). Cannabidiol may also modify the anxiety provoked by pure THC administration (18). It is well known that herbal cannabis originating from different geographical regions may contain different profiles of cannabinoids (19), and hashish, the compressed resins synthesized on the flowering heads, may also contain cannabinoid profiles that are different from those of herbal cannabis (20). Thus, the source of the cannabis used by patients may affect not only the dose but also the response. Third, it is not known whether the dose used for therapeutic effect is associated with the severity of pain or with other behavioural or biological factors. Many patients may have had prior experience with cannabis use recreationally (21), which may change their expectation of the drug's effect (22).

Despite this variability, the doses used among the patients in this survey tended to be modest. Some patients used cannabis at a dose of one joint at night, while daytime users smoked fewer puffs more frequently. A total daily dose of one joint per day, either as one dose or in divided doses, appeared to be most common in our patients. The long term effects of this level of exposure to smoked cannabis on the respiratory and other systems are not well known.

In summary, many pain practitioners across Canada will have encountered patients who are either already using cannabis for pain relief or who, in light of recent media interest in medical cannabis issues, will present to their physicians requesting advice or further information. A useful background on cannabinoids has appeared in a previous issue of *Pain Research & Management* (23). With the belief that some information is better than none, we hope that this series of 15 patients with a variety of pain syndromes who reported their experience of cannabis use for symptom management will be of some use in guiding the sort of questions to ask. Our data suggest that dose sizes may be measured in puffs, and that pain relief is one of several possible outcomes that chronic pain patients are seeking to achieve with cannabis use.

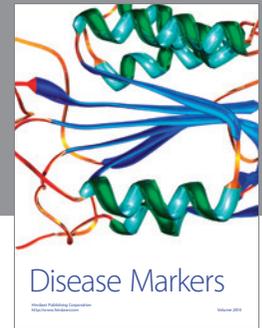
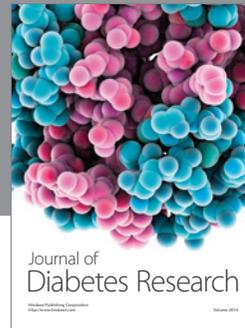
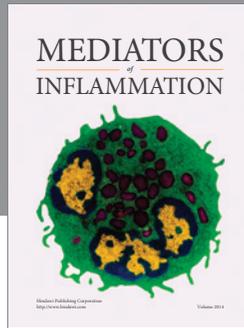
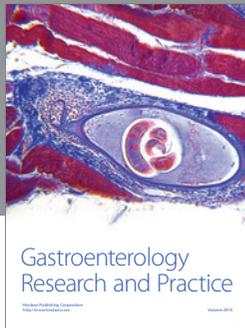
We would like to make three suggestions for further research. First, large, prospective questionnaire studies are required to determine the prevalence of cannabis use among patients with chronic pain, and to ascertain the number of patients who have tried cannabis but not found it useful. Second, more detailed data on the dose (size and frequency), and the perceived benefits and side effects of cannabis use are required. We believe that therapeutic cannabis users are a useful potential source of this information, and we suggest that these data may be collected with

the help of the Compassion Club community, where thousands of Canadians are currently obtaining cannabis for therapeutic purposes. Third, the cohort of patients using cannabis under the Medical Marijuana Access Regulations offers a unique opportunity to collect prospective dose and outcome data. Once a standardized cannabis material is available to these patients, some of the inherent variability in dose estimates may be minimized.

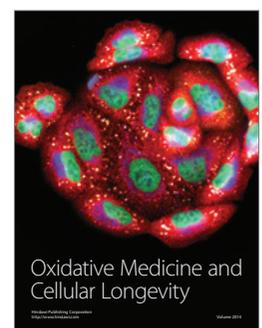
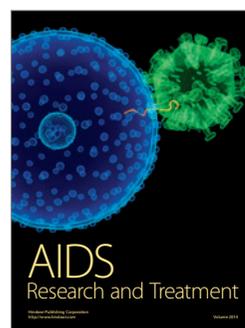
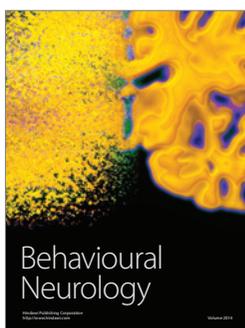
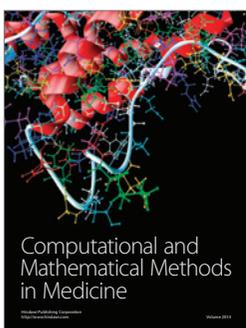
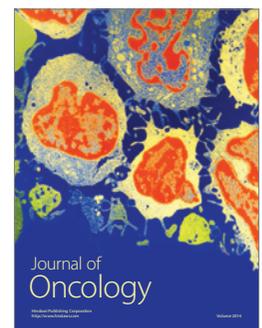
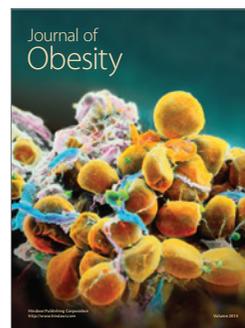
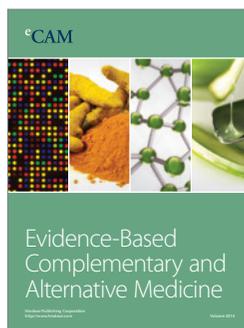
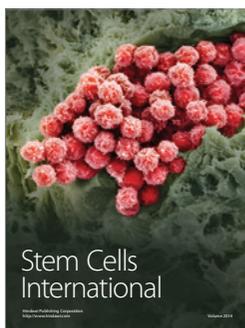
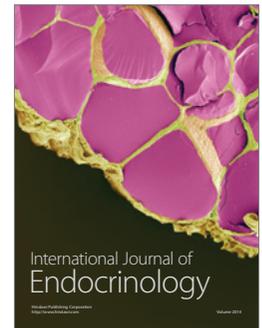
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REFERENCES

1. Wills S. Cannabis use and abuse by man: an historical perspective. In: Brown DT, eds. *Cannabis: The Genus Cannabis*. Amsterdam: Harwood Academic Publishers, 1998:1-27.
 2. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* 1990;346:561-4.
 3. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 1993;365:61-5.
 4. Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 1992;258:1946-9.
 5. Martin BR, Mechoulam R, Razdan RK. Discovery and characterization of endogenous cannabinoids. *Life Sci* 1999;65:573-5.
 6. Meng ID, Manning BH, Martin WJ, Fields HL. An analgesia circuit activated by cannabinoids. *Nature* 1998;395:381-3.
 7. Favorable Medical Marijuana Polls 1995-1999. <<http://www.norml.org/medical/polls.shtml>> (Version current at February 27, 2002)
 8. Health Canada. Medical Marijuana Research Plan. <http://www.cihhr.ca/funding_opportunities/cihhr_funding_pgms/req_for_proposal/rfpmarijuana_e.shtml> (Version current at June 4, 2001)
 9. Richardson JD. Cannabinoids modulate pain by multiple mechanisms of action. *J Pain* 2000;1:2-14.
 10. Noyes R Jr, Brunk SF, Avery DAH, Canter AC. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clin Pharmacol Ther* 1975;18:84-9.
 11. Holdcroft A, Smith M, Jacklin A, et al. Pain relief with oral cannabinoids in familial Mediterranean fever. *Anaesthesia* 1997;52:483-6.
 12. Grinspoon L, Bakalar JB. *Marihuana, the Forbidden Medicine*. New Haven: Yale University Press, 1997.
 13. Huestis MA, Henningfield JE, Cone EJ. Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. *J Anal Toxicol* 1992;16:276-82.
 14. Farnsworth DL. What is the evidence for an amotivational syndrome in cannabis users? *Ann NY Acad Sci* 1976;282:1.
 15. Solowij N. Do cognitive impairments recover following cessation of cannabis use? *Life Sci* 1995;56:2119-26.
 16. Vainio A, Ollila J, Matikainen E, Rosenberg P, Kalso E. Driving ability in cancer patients receiving long-term morphine analgesia. *Lancet* 1995;346:667-70.
 17. Malfait AM, Gallily R, Sumariwalla PF, et al. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritis therapeutic in murine collagen-induced arthritis. *Proc Natl Acad Sci USA* 2000;97:9561-6.
 18. Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology (Berl)* 1982;76:245-50.
 19. Brenneisen R, ElSohly MA. Chromatographic and spectroscopic profiles of Cannabis of different origins: Part I. *J Forensic Sci* 1988;33:1385-404.
 20. Michoulam R, Shvo Y, Hashish I. The structure of cannabidiol. *Tetrahedron* 1963;19:2073-8.
 21. Osborne AC, Smart RG. Cannabis users in the general Canadian population. *Subst Use Misuse* 2000;35:301-11.
 22. Vogel-Sprott M, Fillmore MT. Expectancy and behavioural effects of socially used drugs. In: Kirsch I, ed. *How Expectancies Shape Experience*. Washington: American Psychological Association, 1999:215-32.
 23. Cannabinoids. Proceedings of the inaugural meeting of the Canadian Consortium for the Investigation of Cannabinoids in Human Therapeutics. May 25-26, 2001 Halifax, Nova Scotia. *Pain Res Manage* 2001;6:57-112.
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The Effects of Nabilone on Sleep in Fibromyalgia: Results of a Randomized Controlled Trial

Mark A. Ware, MBBS, MSc,
MRCP*†

Mary-Ann Fitzcharles, MBBS,
FRCPC‡

Lawrence Joseph, PhD§

Yoram Shir, MD*†

BACKGROUND: Sleep disorders affect many patients with chronic pain conditions. Cannabis has been reported by several patient populations to help sleep. We evaluated the safety and efficacy of nabilone, a synthetic cannabinoid, on sleep disturbance in fibromyalgia (FM), a disease characterized by widespread chronic pain and insomnia.

METHODS: We conducted a randomized, double-blind, active-control, equivalency crossover trial to compare nabilone (0.5–1.0 mg before bedtime) to amitriptyline (10–20 mg before bedtime) in patients with FM with chronic insomnia. Subjects received each drug for 2 wk with a 2-wk washout period. The primary outcome was sleep quality, measured by the Insomnia Severity Index and the Leeds Sleep Evaluation Questionnaire. Secondary outcomes included pain, mood, quality of life, and adverse events (AEs).

RESULTS: Thirty-one subjects were enrolled and 29 completed the trial (26 women, mean age 49.5 yr). Although sleep was improved by both amitriptyline and nabilone, nabilone was superior to amitriptyline (Insomnia Severity Index difference = 3.2; 95% confidence interval = 1.2–5.3). Nabilone was marginally better on the restfulness (Leeds Sleep Evaluation Questionnaire difference = 0.5 [0.0–1.0]) but not on wakefulness (difference = 0.3 [–0.2 to 0.8]). No effects on pain, mood, or quality of life were observed. AEs were mostly mild to moderate and were more frequent with nabilone. The most common AEs for nabilone were dizziness, nausea, and dry mouth.

CONCLUSIONS: Nabilone is effective in improving sleep in patients with FM and is well tolerated. Low-dose nabilone given once daily at bedtime may be considered as an alternative to amitriptyline. Longer trials are needed to determine the duration of effect and to characterize long-term safety.

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Fibromyalgia (FM) is a chronic pain syndrome characterized by diffuse body pain with associated pressure allodynia. The diagnosis is clinical with no confirmatory test and is based on a history of widespread pain and the presence of tenderness at 11 of 18

specific tender point sites.¹ This condition, predominantly affecting adult women, is worldwide and common with a prevalence of 2% in North America.^{2–4}

Although the pathophysiology of FM is not clearly understood, evidence is emerging of widespread central nervous system sensitization,⁵ which may be mediated by dopaminergic,⁶ serotonergic,⁷ and glutamatergic⁸ mechanisms. Autonomic dysregulation has also been postulated in FM.^{9–11}

In addition to the report of pain, patients with FM experience numerous other somatic symptoms such as fatigue, mood disorder, and sleep disturbance that have an important effect on well-being. Insomnia has been reported in >75% of patients with FM.¹² Unique sleep patterns have been identified in patients with FM, for example, increased α non-rapid eye movement (REM) spindles on electroencephalogram recordings.¹³ The use of antidepressant therapy has been shown to improve sleep quality in patients with FM.¹⁴

Pregabalin has been shown to be effective for pain in FM¹⁵ and was recently approved by the United States Food and Drug Administration for the management of pain associated with FM. Before this, standard treatment for FM has included low-dose tricyclic antidepressants such as amitriptyline, cardiovascular

From the *Pain Clinic, McGill University Health Centre; †Alan Edwards McGill Centre for Research on Pain; ‡Division of Rheumatology, and §Department of Biostatistics and Epidemiology, McGill University, Montreal, Quebec, Canada.

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MW conceived of, designed, and supervised the trial and wrote the first draft of the manuscript. MAF and YS contributed to study design and conduct. LJ prepared the statistical plan and conducted the analyses. All authors contributed to writing the study report. MW had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Address correspondence and reprint requests to Dr. Mark A. Ware, E19.145 Montreal General Hospital, 1650 Cedar Ave., Montreal, Quebec, Canada H3G 1A4. Address e-mail to mark.ware@muhc.mcgill.ca.

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exercise, cognitive behavioral therapy, and patient education.^{16,17} Nabilone, a synthetic cannabinoid, has been observed in a small case series to improve sleep in patients with chronic pain.¹⁸ A recent small randomized controlled trial of nabilone in FM was shown to reduce pain, but sleep changes were not reported.¹⁹ To our knowledge, no study has specifically evaluated sleep quality as a primary outcome in FM. This study was therefore designed to investigate the effects of nabilone on sleep in patients with FM.

METHODS

We conducted a randomized, active-control, equivalence clinical trial using a 2-period crossover design. Each period was of 2 wk duration separated by a 2-wk washout phase. The total study period was for 10 wk, including the initial and final 2-wk washout periods.

Participants

Subjects were recruited from the Pain Clinic of the McGill University Health Centre. Eligible subjects were adult men and nonpregnant women aged 18 yr or older with a diagnosis of FM¹ who had self-reported chronic insomnia. Insomnia was defined as disturbed sleep either every night or every other night for the past 6 mo.²⁰ Subjects remained on stable analgesic therapy and had to have a negative urine screen for cannabinoids at the baseline visit. Subjects who were using a cannabinoid or amitriptyline at screening underwent a 2-wk washout period before entering the study. Subjects were excluded if they had cancer pain, unstable cardiac disease, a history of psychotic disorder, schizophrenia, or recent manic episode (within the past year), seizure disorder, glaucoma, urinary retention, hypersensitivity to cannabinoids, amitriptyline, or related tricyclic antidepressants, or were taking monoamine oxidase inhibitors.

Eligible and consenting subjects underwent a medical history, physical examination, and chart review. Vital signs and concomitant medications were recorded, and urinary drug screening, full blood counts, and renal and liver function tests were performed and required to be negative or normal. At the baseline visit, eligible subjects completed questionnaires on pain, mood, and quality of life (see below), and underwent a urine drug test before randomization.

Study Drug

Doses of nabilone 0.5 mg or amitriptyline 10 mg were prepared by an independent pharmacy in sealed opaque capsules. Subjects received either nabilone 0.5 mg or amitriptyline 10 mg at the start of the treatment cycle of the study according to the randomization schedule. On Day 7 of each treatment cycle, the study physician evaluated whether the subject might benefit from an increase in dose. If an increase was indicated, the dose of the assigned medication was doubled (to either nabilone 1 mg or amitriptyline 20 mg) for the second week. At the end of the second week, subjects

stopped the study medication for a 2-wk washout period and began the second treatment cycle on the other study drug following the same procedures as above.

Objectives

The primary objective of this study was to determine whether nabilone is equivalent to amitriptyline in improving quality of sleep in patients with FM. The secondary objective was to describe the effects of nabilone on the other clinical variables of pain, mood, quality of life, and global satisfaction. Adverse events (AEs) were recorded.

Study Outcomes

Primary Outcome

The primary outcome was the quality of sleep. Two measures were used to assess sleep, the Insomnia Severity Index (ISI) and the Leeds Sleep Evaluation Questionnaire (LSEQ). The ISI is a reliable and valid instrument used to quantify perceived insomnia severity and is used as an outcome measure in insomnia treatment research.²¹ A score of <8 on the ISI implies no clinical insomnia, 8–14 implies moderate insomnia, and >15 implies severe insomnia. The LSEQ is a well-validated instrument that has been used to monitor subjectively perceived changes in sleep during psychopharmacological investigations with a variety of psychoactive drugs including sedative hypnotics, anxiolytics, central nervous system stimulants, and antihistamines.²² The LSEQ comprises ten 100-mm visual analog scales measuring 4 characteristics of sleep: getting to sleep, quality of sleep, awakening from sleep, and behavior after wakefulness. We used the full LSEQ at clinic visits and in a study diary. During telephone interviews, patients responded to the questions on a 0–10 numerical scale. Sleep diaries were completed daily and returned at the end of each 2-wk cycle. Sleep data were also collected on 3 occasions by telephone during each week of the study including the washout period.

Secondary Outcomes

The secondary outcomes were pain, mood, quality of life, global satisfaction with treatment, and AEs. Pain was measured with the McGill Pain Questionnaire, a widely used and validated instrument frequently used in clinical trials of analgesic medications.²³ Mood was assessed using the short-form Profile of Mood States.²⁴ Quality of life was assessed using the Fibromyalgia Impact Questionnaire, a validated and disease-specific questionnaire for FM.²⁵ Patient global satisfaction was assessed using the question “Would you wish to continue with this medication?” (Y/N). Data on pain, mood, quality of life, and satisfaction were collected on Days 1 and 14 of each treatment cycle. At the end of the third and last washout phase, patients were asked to give their preference (if any) for 1 of the study

medications. Vital signs were recorded at each clinic visit. AEs were recorded throughout the study.

Urine samples were obtained at the screening visit and on Days 1 and 14 of each treatment cycle and tested by semiquantitative assay for the principal urinary metabolite (9-COOH-THC) of tetrahydrocannabinol (THC) to ensure that no other cannabinoid was used during the study.

Sample Size Estimation

The LSEQ has demonstrated differences in sleep quality from baseline of >1.5 on a 10-cm scale with samples of 30 subjects or fewer.²² An equivalence study comparing the analgesic efficacy of amitriptyline with gabapentin concluded equivalence with 24 subjects. There are no specific data on sleep scores after amitriptyline therapy. We therefore estimated that a sample of 30 subjects would be sufficient to conclude equivalence based on within-subject *SD* of 1.0 around the primary outcome, because this would provide a confidence interval (CI) width for the between-treatment difference of approximately ± 0.7 on the LSEQ scale. To account for a dropout rate of up to 25%, we aimed to recruit 40 subjects for this trial for a final sample size of at least 30 subjects. No interim analyses were planned.

Randomization

The randomization schedule was prepared (ralloc procedure, Stata version 8.0, Houston, TX) using randomly assigned block sizes ranging from 2 to 8. The schedule was kept by the study pharmacist away from the investigators. Study subjects were consecutively assigned to treatment order by the study nurse based on the randomization schedule. A coded script was given to the subject with instructions on the use of the allocated treatment. The subject then collected the medication from the study pharmacy and began taking the medication the same night.

Blinding

The study physician, study nurse, and subjects were blinded to the allocated treatment order. At the end of the study, the subjects were asked to estimate the order of allocated drugs as a means of estimating the success of blinding.

Statistical Analyses

The principal hypothesis for this study was that nabilone at a dose of 0.5–1 mg is equivalent to amitriptyline at a dose of 10–20 mg in improving sleep quality in patients with FM. The primary outcome of sleep quality was derived from the average scores obtained during the second week of each cycle of the ISI and of the sleep quality items (questions 4 and 5 on restfulness and wakefulness, respectively) from the LSEQ. The sleep scores during nabilone therapy were compared with those during amitriptyline using CIs of the within-subject difference in scores. Regression models were created with treatment, period, and

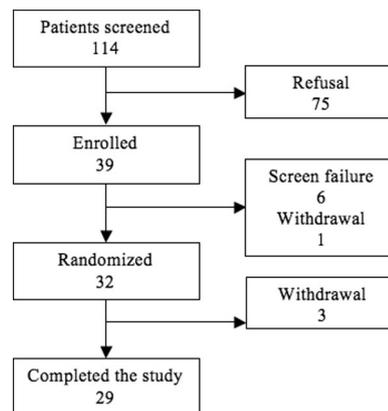


Figure 1. Trial flow diagram.

Table 1. Baseline Demographic Characteristics of Trial Participants ($n = 32$)

Characteristic	
Mean age (SD), range (yr)	49.5 (11.2), 26–76
Gender	
Female	26
Male	5
Education level attained	
University/college	25
Secondary/high school	6
Primary/elementary	1
Employment status	
Full time employed	12
Retired	6
Long term disability	4
Short term disability	4
Part time employed	2
Home maker	2
Other	2

order as terms in the model. Examination of treatment by period interactions was included to assess potential carryover effects. For inferences, 95% CIs were generated for all parameters. Secondary outcomes were assessed using similar procedures for each variable. AEs were tabulated by severity and study drug.

Ethics and Trial Registration

Ethics approval was obtained from the McGill University Health Centre Research Ethics Board; all subjects provided written informed consent. Approval to use the study drugs was obtained through a Clinical Trial Application to the Therapeutic Products Directorate of Health Canada (Clinical Trial Application number 099547). The trial was conducted following Good Clinical Practice guidelines and was registered at www.clinicaltrials.gov (registration number NCT00381199).

RESULTS

One hundred fourteen subjects were screened, 39 were enrolled, and 32 were recruited and randomized to study drug (Fig. 1). Enrollment began in August 2005 and the last enrolled subject completed follow-up

Table 2. Baseline Self-Reported Symptom Data for Study Participants ($n = 32$)

Variable	Mean	SD
Insomnia severity index	18.3	5.2
McGill pain questionnaire		
Present pain intensity (PPI)	2.3	0.8
Sensory	15.8	9.0
Affective	4.7	3.1
Evaluative	2.3	1.3
Miscellaneous	6.0	3.0
Fibromyalgia impact questionnaire total score	62.6	15.2
Rested	81.6	15.3
Fatigue	80.5	20.2
Stiffness	74.5	19.5
Pain	69.3	20.5
Do work	66.4	25.1
Anxiety	51.6	30.1
Depression	37.5	32.5
Feel good	5.3	1.6
Physical impairment	1.4	0.8
Work missed	0.4	0.5
Profile of mood states total score	29.5	16.6
Fatigue	10.6	4.3
Tension/anxiety	7.3	3.7
Depression	5.8	4.4
Confusion	5.6	2.9
Anger	5.2	4.0
Vigor	4.6	3.3

Note the Leeds Sleep Evaluation Questionnaire is not measured at baseline because it requires a comparison with normal sleep.

in January 2007. Three subjects withdrew after randomization, 1 for noncompliance with study protocol, 1 for lack of effect, and 1 because of side effects after a single dose (edema of arms and legs, decreased concentration, dizziness, nausea, hyper-alert state, and insomnia). Twenty-nine subjects completed the study per protocol; there were no dropouts. All randomized subjects' data were included in the safety analysis.

Of the 32 randomized subjects, 26 were women and 5 were men (1 missing data). The mean age was 49.5 yr (SD 11.2) with a range of 26–76 yr. Baseline demographic and clinical data of recruited subjects are shown in Tables 1 and 2. Five subjects were taking

tricyclic antidepressants at screening (4 amitriptyline and 1 nortriptyline), and all successfully withdrew from these medications before randomization. No subject was taking cannabinoid medications at screening, and all baseline urine tests were negative for THC.

Primary Outcome

Although both drugs improved sleep, after controlling for period effects, nabilone was found to have a greater effect on sleep than amitriptyline on the ISI (adjusted difference = -3.25 ; CI, -5.26 to -1.24) (Fig. 2). Based on the LSEQ sleep quality outcomes, there was no evidence of superiority of either drug, although subjects had a more restful sleep taking nabilone compared with amitriptyline (difference = 0.48 ; CI, 0.01 – 0.95) (Fig. 3). There were no marked differences in other scales of the LSEQ between the 2 drugs, although there was a suggestion of nabilone performing better than amitriptyline for ease (difference = -0.7 ; CI, -1.4 to 0.02) and speed (difference = -0.7 ; CI, -1.36 to 0.03) of falling asleep.

Other Outcomes

No differences were noted between treatments for pain (McGill PPI difference = -0.1 ; 95% CI = -0.3 to 0.2 ; other scales of McGill Pain Questionnaire also not significant), mood (Profile of Mood States difference = 1.4 ; 95% CI = -4.3 to 7.2), or quality of life (Fibromyalgia Impact Questionnaire difference = -0.7 ; 95% CI = -7.3 to 5.8).

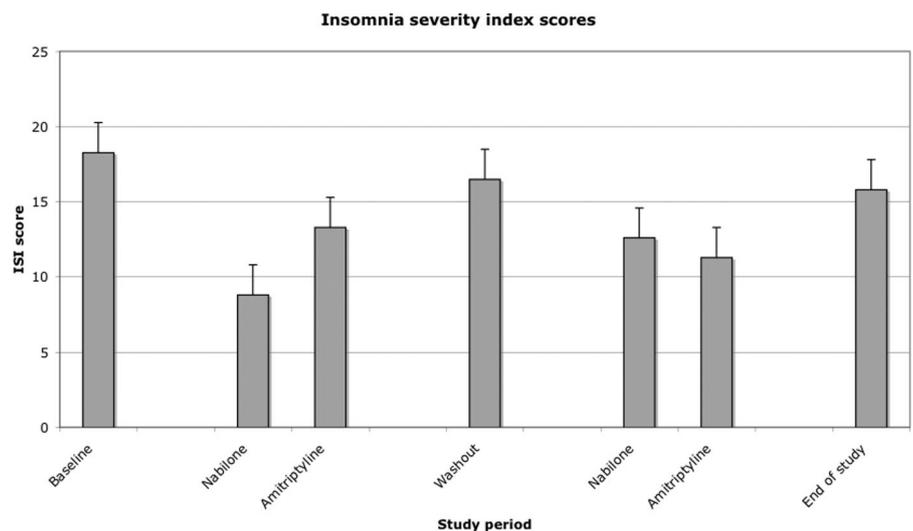
Satisfaction and Preference

At the completion of the trial, preference for nabilone was reported by 41% (12 of 29) and for amitriptyline by 32% (9 of 28) of subjects (difference = 9%; 95% CI = -16% to 32%).

Dose Adjustment

The dose of amitriptyline was more frequently increased at 1 wk (26 of 28; 92%) compared with nabilone (21 of 29; 72%) (difference = 20%; 95% CI = -2% – 43%).

Figure 2. Effects of nabilone and amitriptyline on the Insomnia Severity Index (ISI).



Treatment Effect [LSEQ]

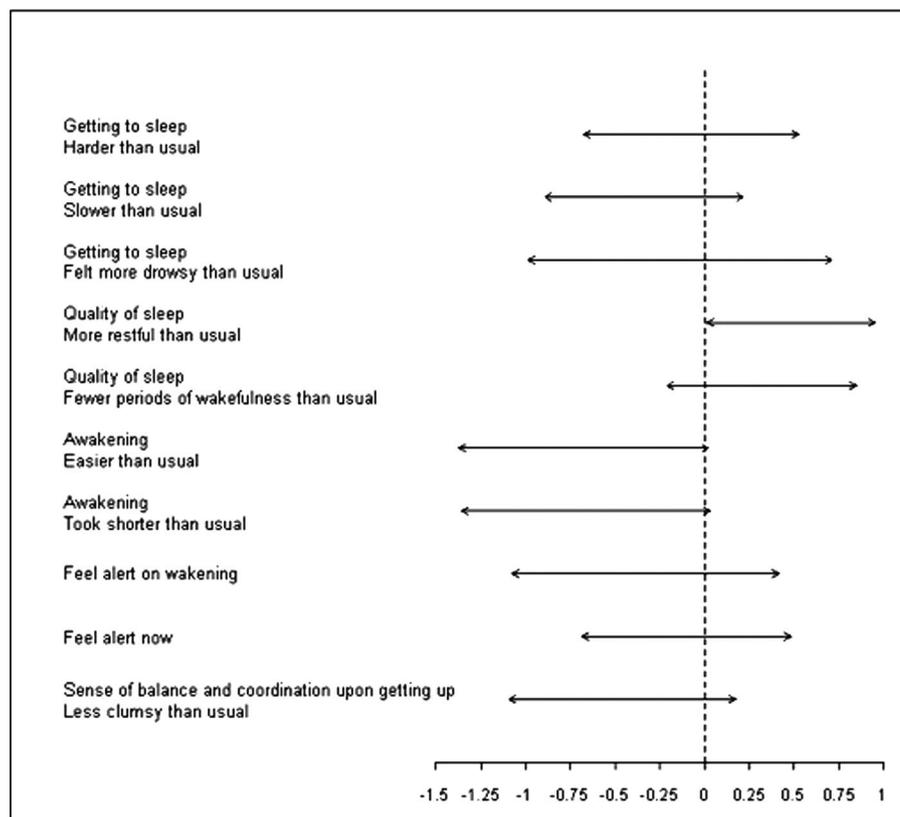


Figure 3. Treatment effects of nabilone compared with amitriptyline on sleep items in the Leeds Sleep Evaluation Questionnaire (LSEQ). Note that treatment effects shifted to the right favor nabilone, whereas effects shifted to the left favor amitriptyline. The *x* axis is the magnitude of the effect on a scale from 0 to 10. Shifts to the right represent improvements on the sleep subscales (shown on the *y* axis).

Table 3. Absolute Number of Adverse Events Occurring on >1 Occasion During the Trial

Description	Nabilone	Amitriptyline	Total
Dizziness	10	4	16
Headache	4	6	14
Nausea	9	1	14
Dry mouth	7	3	10
Drowsiness	6	1	7
Constipation	4	1	5
Diarrhea	2	2	4
Insomnia	3		3
Vomiting	3		3
Blurred vision	2	3	5
Fatigue	2	1	3
Cognitive impairment	2		2
Disorientation	2		2
Migraine	2		2

Discernment

When asked at the end of the study to guess which treatment had been administered, 8 subjects (29%) correctly identified the period in which they received amitriptyline, and 12 (41%) correctly identified the period in which they received nabilone.

Adverse Events

A total of 187 AEs were reported during the trial of which 120 were mild, 64 were moderate, and 3 severe. Of the 3 severe AEs, 2 occurred during amitriptyline therapy (headache and insomnia) and 1 occurred

during nabilone (drowsiness). No serious AEs occurred during the trial. Fifty-three AEs were deemed possibly or probably related to amitriptyline therapy, and 91 AEs were deemed possibly or probably related to nabilone therapy. The most common AEs reported for nabilone and amitriptyline are shown in Table 3. AEs occurring in >2 subjects, which were more common for nabilone, were dizziness (10 subjects), nausea (9), dry mouth (7), drowsiness (6), constipation (4), insomnia (3), and vomiting (3).

DISCUSSION

We have observed that both the synthetic cannabinoid nabilone and the tricyclic antidepressant amitriptyline had a favorable effect on sleep in patients with FM, with nabilone showing overall superiority to amitriptyline for sleep quality. The effects of nabilone on pain, mood, and quality of life were similar to those seen with amitriptyline. Adverse effects were more common with nabilone, particularly drowsiness and dizziness, although global satisfaction with both drugs was similar.

The effects of cannabinoids on sleep have been recognized for many years. The hypnotic effects of THC were evaluated in the 1970s, and it was shown that THC increased Stage 3 sleep and reduced REM sleep²⁶; amitriptyline has not been found to have any effect on non-REM sleep in patients with FM.²⁷

Researchers conducting clinical trials of cannabinoids for other chronic pain disorders have reported improved sleep as secondary outcomes.²⁸ Endogenous cannabinoids have also been postulated to have an effect on normal sleep induction.²⁹ To our knowledge, this is the first study to evaluate sleep as a primary outcome for a chronic noncancer pain condition.

Our study has several important strengths. First, because both drugs cause similar side effects (e.g., drowsiness and dry mouth), we postulated that amitriptyline would be a suitable active control for nabilone, and therefore would preserve the blinded nature of the trial. Our data on blinding suggest that blinding was preserved, suggesting that amitriptyline is a good active control for further trials of nabilone. Second, because amitriptyline is frequently used for promoting sleep in FM, and because we have observed improvement of sleep among subjects taking amitriptyline, we believe that the study has demonstrated internal and external validity and was sufficiently powered to show clinically meaningful sleep improvements. For these reasons, we believe that the effects of nabilone on sleep quality are valid.

There are a number of limitations to this study that require comment. First, because the exposure to each drug was for a single 2-wk period, we are unable to extrapolate any conclusions regarding the long-term safety and efficacy of nabilone for sleep disturbance in FM. Because FM is a chronic condition, favorable treatments will likely require prolonged administration. Second, because both study drugs were used in relatively low dosage, this may have influenced the final outcome either favorably for nabilone (if nabilone was more effective at lower doses) or unfavorably for amitriptyline (if amitriptyline was more effective at higher doses). Because no other equivalency studies have previously been conducted with these drugs, the selected doses of the study drugs were based on clinical experience. Further dose-finding studies, specifically for nabilone, may be needed to explore safety and efficacy if higher doses are to be considered.

The mainstay of management for FM remains a multidisciplinary treatment approach, which includes exercise, education, pharmacological interventions, and behavioral therapies.^{17,30} Sleep disturbances in FM are associated with poor quality of life and function, and increased pain and fatigue.³¹ Although nabilone has been shown to have analgesic effects on pain in FM,¹⁹ the effects of nabilone on sleep have not hitherto been addressed in this population.

In conclusion, we report that the synthetic cannabinoid nabilone is an effective drug in promoting sleep in patients with FM who have chronic insomnia and may be superior to amitriptyline, which is currently widely used for this purpose. Further studies on

the effects of nabilone on sleep architecture and long-term safety and efficacy in FM and other pain conditions are warranted.

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REFERENCES

1. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990;33:160–72
2. White KP, Speechley M, Harth M, Ostbye T. The London Fibromyalgia Epidemiology Study: the prevalence of fibromyalgia syndrome in London, Ontario. *J Rheumatol* 1999;26:1570–6
3. McNally JD, Matheson DA, Bakowsky VS. The epidemiology of self-reported fibromyalgia in Canada. *Chronic Dis Can* 2006;27:9–16
4. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 1995;38:19–28
5. Staud R. New evidence for central sensitization in patients with fibromyalgia. *Curr Rheumatol Rep* 2004;6:259
6. Wood PB, Schweinhardt P, Jaeger E, Dagher A, Hakyemez H, Rabiner EA, Bushnell MC, Chizh BA. Fibromyalgia patients show an abnormal dopamine response to pain. *Eur J Neurosci* 2007;25:3576–82
7. Seidel MF, Weinreich GF, Stratz T, Muller W. 5-HT₃ receptor antagonists regulate autonomic cardiac dysfunction in primary fibromyalgia syndrome. *Rheumatol Int* 2007;27:1025–30
8. Sarchielli P, Di Filippo M, Nardi K, Calabresi P. Sensitization, glutamate, and the link between migraine and fibromyalgia. *Curr Pain Headache Rep* 2007;11:343–51
9. Sarzi-Puttini P, Atzeni F, Diana A, Doria A, Furlan R. Increased neural sympathetic activation in fibromyalgia syndrome. *Ann N Y Acad Sci* 2006;1069:109–17
10. Nilsen KB, Sand T, Westgaard RH, Stovner LJ, White LR, Bang Leistad R, Helde G, Rø M. Autonomic activation and pain in response to low-grade mental stress in fibromyalgia and shoulder/neck pain patients. *Eur J Pain* 2007;11:743–55
11. Martinez-Lavin M, Hermosillo AG. Autonomic nervous system dysfunction may explain the multisystem features of fibromyalgia. *Semin Arthritis Rheum* 2000;29:197–9
12. Drewes AM. Pain and sleep disturbances with special reference to fibromyalgia and rheumatoid arthritis. *Rheumatology (Oxford)* 1999;38:1035–8
13. Drewes AM, Nielsen KD, Taagholt SJ, Bjerregard K, Svendsen L, Gade J. Sleep intensity in fibromyalgia: focus on the microstructure of the sleep process. *Br J Rheumatol* 1995;34:629–35
14. O'Malley PG, Balden E, Tomkins G, Santoro J, Kroenke K, Jackson JL. Treatment of fibromyalgia with antidepressants: a meta-analysis. *J Gen Intern Med* 2000;15:659–66
15. Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE, Young JP Jr, LaMoreaux LK, Martin SA, Sharma U; Pregabalin 1008–105 Study Group. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005;52:1264–73
16. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. *JAMA* 2004;292:2388–95
17. Rooks DS. Fibromyalgia treatment update. *Curr Opin Rheumatol* 2007;19:111–7
18. Berlach DM, Shir Y, Ware MA. Experience with the synthetic cannabinoid nabilone in chronic noncancer pain. *Pain Med* 2006;7:25–9
19. Skrabek RQ, Galimova L, Ethansand Daryl K. Nabilone for the treatment of pain in fibromyalgia. *J Pain* 2008;2:164–73
20. About insomnia. Available at: www.americaninsomniaassociation.org/aboutaia.htm. Accessed November 16, 2007

21. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001;2:297–307
22. Parrott AC, Hindmarch I. The Leeds Sleep Evaluation Questionnaire in psychopharmacological investigations—a review. *Psychopharmacology (Berl)* 1980;71:173–9
23. Melzack R. The short-form McGill Pain Questionnaire. *Pain* 1987;30:191–7
24. Curran SL, Andrykowski MA, Studts JL. Short form of the Profile of Mood States (POMS-SF): psychometric information. *Psychol Assess* 1995;7:80–3
25. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. *J Rheumatol* 1991;18:728–33
26. Feinberg I, Jones R, Walker JM, Cavness C, March J. Effects of high dosage delta-9-tetrahydrocannabinol on sleep patterns in man. *Clin Pharmacol Ther* 1975;17:458–66
27. Carette S, Oakson G, Guimont C, Steriade M. Sleep electroencephalography and the clinical response to amitriptyline in patients with fibromyalgia. *Arthritis Rheum* 1995;38:1211–7
28. Russo EB, Guy GW, Robson PJ. Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. *Chem Biodivers* 2007;4:1729–43
29. Mechoulam R, Fride E, Hanus L, Sheskin T, Bisogno T, Di Marzo V, Bayewitch M, Vogel Z. Anandamide may mediate sleep induction. *Nature* 1997;389:25–6
30. Staud R. Treatment of fibromyalgia and its symptoms. *Expert Opin Pharmacother* 2007;8:1629–42
31. Theadom A, Cropley M, Humphrey KL. Exploring the role of sleep and coping in quality of life in fibromyalgia. *J Psychosom Res* 2007;62:145–51

Minnesota Medical Cannabis Program: Patient Experiences from the First Program Year

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Minnesota Department of Health
Office of Medical Cannabis
PO Box 64882
St. Paul, MN 55164-0882
651-201-5598 (Metro) or 844-879-3381 (Non-metro, toll-free)
Health.Cannabis@state.mn.us
www.health.state.mn.us

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Executive Summary

In May 2014, Minnesota became the 22nd state to create a medical cannabis program. Distribution of extracted cannabis products in liquid or oil form to qualified, enrolled patients began July 1, 2015. Minnesota's medical cannabis program is distinct from those in nearly all other states as the Minnesota Department of Health's Office of Medical Cannabis is required to study and learn from the experience of participants. This report draws on data from enrollment, purchasing and related health information, and survey results to describe the experience of patients who enrolled during the first year of the program's operation: July 1, 2015 through June 30, 2016.

The Office of Medical Cannabis anticipates performing additional analyses of data for the first year cohort of enrolled patients, as well as initiating analyses of data from patients who enrolled in the program later. Of particular interest are patients who enrolled after intractable pain became a qualifying condition on August 1, 2016. A report is planned for the end of 2017 that will give a preliminary look at the experience of the first several hundred patients certified for intractable pain. It is possible that focused projects will be developed in the future that will draw on medical record information to answer specific questions raised by analyses of the kinds of program data described in this report.

Participation

Between July 1, 2015 and June 30, 2016 a total of 1660 patients enrolled in the program and 577 health care practitioners registered themselves in order to certify that patients have a medical condition that qualifies them for the program. The most common qualifying conditions were severe and persistent muscle spasms (43%), cancer (28%), and seizures (20%). Each of the remaining six qualifying conditions during the first year – Crohn's Disease, Terminal illness, HIV/AIDS, Tourette Syndrome, glaucoma, and ALS – accounted for less than 10% of patients. Ten percent (167 patients) were certified for more than one qualifying condition. Most patients were middle-aged (56% between ages 36-64), 11% were <18, and 11% were ≥65. Distribution by race/ethnicity generally matched the state's demographics, with 90% of patients describing themselves as white.

The legislation that established the program specified there would be one location for purchasing medical cannabis (called Cannabis Patient Centers; CPCs) in each of the state's eight congressional districts. Patients who enrolled in the program during the first year came from throughout the state, with the average distance from the patient's home to the nearest CPC 29 miles (median distance=16 miles). Some patients were a considerable distance from the nearest CPC, however, with 13% over 60 miles from the nearest one. The program allows patients to have one or more parents or non-parent caregivers who register with the program, who are then allowed to transport and administer a patient's medical cannabis. Only 11%

of patients had a registered caregiver, 17% had a registered parent or guardian, and 26% had either a registered parent/legal guardian or a registered caregiver.

Among the 577 health care practitioners who registered with the program 82% were physicians, 13% were advanced practice registered nurses, and 5% were physician assistants.

Medical Cannabis Purchasing Patterns

Most patients make their first medical cannabis purchase within 14 days of program approval. Subsequent purchases typically follow a roughly monthly periodicity. However, intervals between purchases are sometimes less than a month, especially during the first months of program participation as the patient experiments with small amounts of different products. And intervals between purchases are sometimes much longer than a month. Using a cutoff of six months without any medical cannabis purchases as a surrogate for program discontinuation, 51% of patients who enrolled and made a purchase within the first six months of the program discontinued participation in the program as of December 31, 2016.

Medical Cannabis Use Patterns

Each patient's medical cannabis purchasing transactions during their first enrollment year (or through early March if still within their first enrollment year) were analyzed. A total of 16,238 products were purchased during 10,898 transactions, with 38% of all transactions consisting of two or more products. For analytic purposes, products were classified according to the ratio of delta-9-tetrahydrocannabinol (THC) to cannabidiol (CBD) as follows: Very High THC:CBD (100:1 or higher), High THC:CBD (>4:1 up to 99:1), Balanced THC:CBD (1:1 up to 4:1), High CBD:THC (\geq 1:1 up to 99:1), and Very High CBD:THC (100:1 or higher).

Products for enteral administration (swallowed – includes capsules and oral solutions) and products for inhalation (vaporized oil) each accounted for 45% of product purchases. Products for oromucosal administration (absorption through cheek) accounted for 9%. Nearly 50% of all purchases were Very High THC:CBD products, followed by Balanced THC:CBD (30%) and High CBD:THC (15%). Very High THC:CBD products were most commonly oil for vaporization or for oromucosal absorption, while Balanced THC:CBD and High CBD:THC products were most often for enteral administration.

Examining purchasing history across all patients is very complex for reasons that include experimentation with different products over time. As a first approach to assessing routine use of products, most frequently purchased products were examined for each patient. For 28% of patients, two or more products were purchased the same number of times. The product types that emerged as most frequently purchased were Very High THC vaporization oil (25%), High CBD:THC enteral preparations (14%), and Balanced enteral preparations (13%). Most frequently purchased product types varied considerably across medical conditions.

Benefits

Information on patient benefits comes from the Patient Self-Evaluations (PSE) completed by patients prior to each medical cannabis purchase and from patient and health care practitioner surveys. Results of analysis of PSE and survey data indicate perceptions of a high degree of benefit for most patients.

Patients responded to a survey question asking them how much benefit they believe they received from using medical cannabis on a scale from 1 (no benefit) to 7 (great deal of benefit). Across all patients 64% indicated a benefit rating of 6 or 7 and this degree of benefit was indicated by at least half of the patients with each medical condition. A small but important proportion of patients indicated little or no benefit: 9% gave a rating of 1, 2, or 3. Benefit ratings varied somewhat by qualifying medical condition. When patients were asked what the most important benefit was for them, two-thirds indicated a reduction in symptoms directly related to their qualifying medical condition and most of the remainder indicated more general quality of life benefits.

An important part of this report is the verbatim comments written by patients, and the reader is encouraged to review these comments, presented in an Appendix. Examples of these comments include:

- “Almost all muscle spasm and pain associated with spasms are gone. I used to have constant nerve triggered pain that is minimal now. Results were almost immediate. I am sleeping way better now also.”
- “[NAME] has passed away. I am her daughter and was her care giver. She was open to trying medical cannabis and we got the liquid form. It was a saving grace. She was in a lot of pain and when prescribed medications did NOT work – we started this and it kept her calm and relaxed. I am very thankful that we were able to have this option available. It helped to make her last months more bearable and truly it would have been miserable without it.”
- “I am getting enough sleep for the first time since about 2011. My absence seizures have gone from 3-4 a day to almost 0. It also has lessened the severity of grand mal seizures. The recovery time after has gone from around 12 hours to around 4.”
- “At first it helped a lot but my seizures have returned.”
- “Spasms – only a little better.”

Health care practitioners were somewhat more conservative in assessment of benefit to their patients. Across all the benefit ratings by health care practitioners, 38% indicated a rating of 6 or 7 and 23% indicated little or no benefit (rating of 1, 2, or 3). Similarity in benefit assessment between health care practitioners and patients appears to vary by medical condition, with highest discrepancy among seizure patients. Descriptive comments suggest at least part of the difference is driven by perspective of what constitutes benefit. The patients cite quality of life

benefits more often than the health care practitioners, who appear to focus more on objective measures such as seizure counts.

The symptom scores provided in the Patient Self-Evaluation data have the advantage of completeness, since they are required prior to each medical cannabis purchase. In this report a reduction of $\geq 30\%$ was applied to most symptoms to indicate clinically meaningful symptom reduction. Results show patterns similar to those in the survey benefits rating, but usually somewhat smaller in size. For most symptoms between half and two-thirds of patients who achieve clinically meaningful improvement retained that degree of improvement over the next four months.

Examples of proportion of patients achieving and retaining $\geq 30\%$ symptom reduction include:

- Among seizure patients, 68% reported $\geq 30\%$ reduction in seizure frequency and 49% both achieved that level of reduction and retained it, on average, for at least four months
- Among patients with Tourette syndrome, 61% reported $\geq 30\%$ reduction in tic frequency and 46% both achieved that level of reduction and retained it, on average, for at least four months
- Among patients with Crohn's disease, 51% reported $\geq 30\%$ reduction in number of liquid stools per day and 29% both achieved that level of reduction and retained it, on average, for at least four months
- Among patients with severe, persistent muscle spasms, 48% reported $\geq 30\%$ reduction in spasm frequency and 28% both achieved that level of reduction and retained it, on average, for at least four months
- Among cancer patients with at least moderate levels of nausea when they started using medical cannabis, 38% reported $\geq 30\%$ reduction of nausea and 23% both achieved that level of reduction and retained it, on average, for at least four months
- Among cancer patients with at least moderate levels of pain when they started using medical cannabis, 29% reported $\geq 30\%$ reduction of pain and 12% both achieved that level of reduction and retained it, on average, for at least four months

Moderate to severe levels of non-disease-specific symptoms such as fatigue, anxiety, and sleep difficulties were common across all the medical conditions. And the reductions in these symptoms was often quite large. These findings support the understanding that some of the benefit perceived by patients is expressed as improved quality of life.

The type(s) of medical cannabis used at the time patients achieved clinically significant improvement was analyzed for each symptom assessed within each category of medical condition. Full results of these analyses are presented in an Appendix and summaries are in the Benefits chapter.

Adverse Side Effects

At this point, the safety profile of the medical cannabis products available through the Minnesota program seems quite favorable. Approximately 20-25% of enrolled patients report negative physical or mental side effects of some kind, with the majority – around 60% - reporting only one and 90% reporting three or fewer. The vast majority of adverse side effects, around 90%, are mild to moderate in severity. An assessment of the 30 patients reporting severe side effects, meaning “interrupts usual daily activities,” found no apparent pattern of patient age, medical condition, or type of medical cannabis used. The most common adverse side effects are dry mouth, drowsiness, and fatigue. Fortunately, up to the present no serious adverse events (life threatening or requiring hospitalization) have been reported.

Affordability and Suggestions for Improving the Program

Unlike traditional pharmaceuticals whose costs are often covered through insurance reimbursement, medical cannabis purchased through the Minnesota program is currently not covered by insurance and must be purchased out of pocket. The patient survey asked for a rating of product affordability on a scale of 1 (very affordable) to 7 (very prohibitive). More than half (51%) responded with a 6 or a 7 and 86% responded with a score of 4 or higher. “Bring the costs down” was a frequent response when patients and certifying health care practitioners were asked how the program could be improved. Some patients indicated on surveys they used less medical cannabis than they knew was helpful to them because they could not afford it.

1. Introduction

In May 2014, Minnesota became the 22nd state to create a medical cannabis program. Distribution of cannabis products to qualified, enrolled patients began July 1, 2015. Minnesota's medical cannabis program is distinct from those in nearly all other states due to the fact that the Minnesota Department of Health's Office of Medical Cannabis is required to study and learn from the experience of participants. Minnesota's online registry, which integrates information from patients, certifying health care practitioners and manufacturers, continuously captures program data. Data elements from the Registry have been selected to create a de-identified research data set for reporting and research. This report draws on aspects of that research data set to describe the experience of patients who enrolled during the first year of the program's operation: July 1, 2015 through June 30, 2016.

Data in this report come from several aspects of the program's operations:

- Information from registration or enrollment of patients, health care practitioners, and caregivers;
- Information patients provide each time they visit a cannabis patient center for purchase of cannabis products, including information on symptom severity and side effects;
- Details about each cannabis product purchased; and
- Information is derived from responses to periodic surveys of patients and their certifying health care practitioners.

Though there is certainly imprecision in some of the data collected by the program, this report provides important details that can be found in few other states. A notable part of the report is a set of statements regarding benefits, negative effects, and comments about the program made by patients and health care practitioners. These are redacted to protect privacy, but otherwise presented as was written on the surveys. The comments have been coded by type but the verbatim comments have a power of their own, reminding us that each enrollee is a unique individual, not just a number. A few comments are included elsewhere, but the reader is encouraged to spend time reviewing the full listing of responses in the appendices.

The Office of Medical Cannabis anticipates performing additional analyses of data for the first year cohort of enrolled patients, as well as initiating analyses of data from patients who enrolled in the program later. Of particular interest are patients who enrolled after intractable pain became a qualifying condition on August 1, 2016. A report is planned for the end of 2017 that will give a preliminary look at the experience of the first several hundred patients certified for intractable pain. It is possible that focused projects will be developed in the future that will

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draw on medical record information to answer specific questions raised by analyses of data derived from the program registry.

2. Patients and Caregivers Registered in the First Program Year

DESCRIPTION OF PATIENTS ENROLLED IN THE FIRST PROGRAM YEAR

Qualifying Condition

During the first year of the Minnesota Medical Cannabis program (July 2015-June 2016), 1,660 patients were certified by registered healthcare practitioners and subsequently enrolled in the program (Figure 2.1). The healthcare practitioners certified the patients as having one or more of the following qualifying conditions: severe and persistent muscle spasms (n=713), cancer (n=468), seizures, including those characteristic of epilepsy (n=328), Crohn's disease (n=108), terminal illness (n=94), HIV/AIDS (n=54), Tourette syndrome (n=30), glaucoma (n=24), and amyotrophic lateral sclerosis (ALS) also known as Lou Gehrig's disease (n=22) (Table 2.1, Figure 2.2). Of the 1660 patients from the first program year, 167 (10.1%) were certified as having more than one qualifying condition; these patients are represented more than once in Table 2.1 and Figure 2.2.

Figure 2.1. Patient enrollment in the first program year.

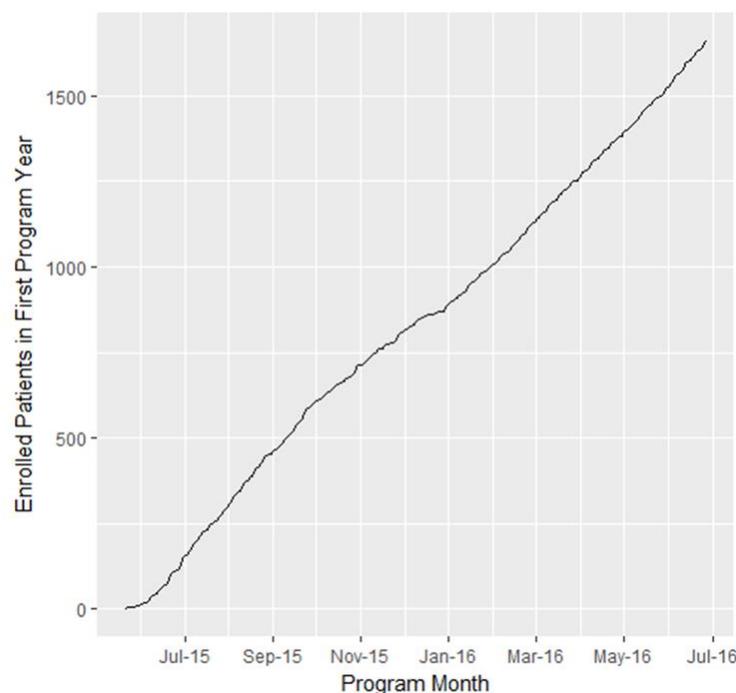
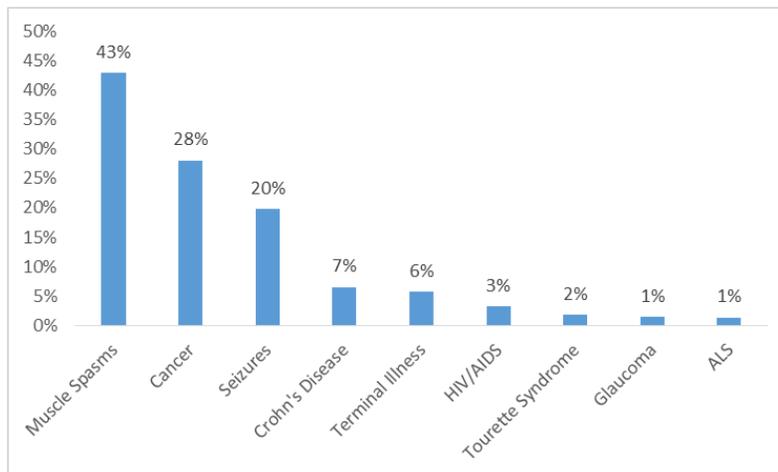


Table 2.1. Patient counts by qualifying condition.

Condition	Count	%
<i>Muscle Spasms</i>	713	43%
<i>Cancer</i>	466	28%
<i>Seizures</i>	328	20%
<i>Crohn's Disease</i>	108	7%
<i>Terminal Illness</i>	94	6%
<i>HIV/AIDS</i>	54	3%
<i>Tourette Syndrome</i>	30	2%
<i>Glaucoma</i>	24	1%
<i>ALS</i>	22	1%

Note: Percentages sum to more than 100 percent because among the 1660 patients enrolled during the first year, 167 (10.1%) were certified for more than one qualifying condition.

Figure 2.2. First year cohort patients by qualifying medical condition.



Note: Percentages sum to more than 100 percent because among the 1660 patients enrolled during the first year, 167 (10.1%) were certified for more than one qualifying condition.

Age and Gender

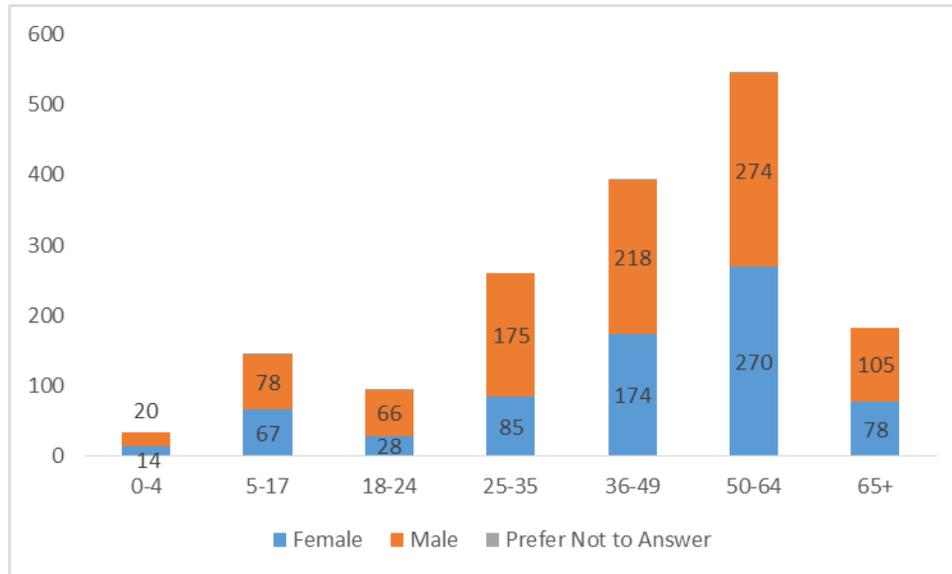
At the time of certifying that a patient has a medical condition qualifying them for the medical cannabis program, the certifying healthcare practitioner enters the patient’s date of birth. Additionally, during registration, patients are asked to report gender and race/ethnicity but are not required to do so. Table 2.2 shows the breakdown of patients by age category and gender at the time of initial program enrollment. The gender breakdown of patients in the first program year was 57% male and 43% female, with <1% of patients declining to report gender. Patients tended to be middle-aged, with 56.3% of the cohort falling between ages 36-64. However, the cohort also included a notable proportion of pediatric patients (10.7%) and patients over 65 years (11.0%).

Table 2.2. Patient counts by age and gender.

	0-4	5-17	18-24	25-35	36-49	50-64	65+
Female	14 (41%)	67 (46%)	28 (29%)	85 (33%)	174 (44%)	270 (49%)	78 (43%)
Male	20 (59%)	78 (53%)	66 (69%)	175 (67%)	218 (55%)	274 (50%)	105 (57%)
Prefer Not to Answer	0 (0%)	1 (1%)	2 (2%)	0 (0%)	2 (1%)	3 (1%)	0 (0%)
Total	34 (2%)	146 (9%)	96 (6%)	260 (16%)	394 (24%)	547 (33%)	183 (11%)

Note: Percentages are calculated based on the total count of patients in each age category.

Figure 2.3. Age and gender breakdown of first year cohort.



Age by Qualifying Condition

Breakdown of age category within each qualifying condition is shown in Table 2.3. Among the first year cohort, average age was 44.3 ± 18.9 years. Age distribution varied substantially across qualifying medical condition groups; patients certified for glaucoma or ALS tended to be older in general (average age of 60.4 ± 14.0 and 61.5 ± 9.6 , respectively); patients certified for seizure disorders or Tourette syndrome generally were younger (23.4 ± 16.0 and 25.3 ± 11.7 , respectively).

Table 2.3. Patient age by qualifying medical condition.

	0-4	5-17	18-24	25-35	36-49	50-64	65+	Mean Age (SD)	Total
Muscle Spasms	3 (0%)	6 (1%)	33 (5%)	124 (17%)	216 (30%)	268 (38%)	63 (9%)	47.3 (14.5)	713
Cancer	3 (1%)	15 (3%)	11 (2%)	33 (7%)	83 (18%)	217 (47%)	104 (23%)	54.6 (16.2)	466
<i>Pain</i>	1 (0%)	3 (1%)	8 (3%)	26 (8%)	65 (20%)	151 (47%)	66 (21%)	54.3 (15.3)	320

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	0-4	5-17	18-24	25-35	36-49	50-64	65+	Mean Age (SD)	Total
<i>Nausea/Vomiting</i>	1 (0%)	12 (4%)	10 (4%)	18 (7%)	50 (18%)	130 (48%)	52 (19%)	53.4 (16.5)	273
<i>Cachexia/Wasting</i>	1 (1%)	6 (3%)	5 (3%)	8 (4%)	16 (9%)	90 (50%)	54 (30%)	57.9 (16.5)	180
Seizures	30 (9%)	114 (35%)	43 (13%)	68 (21%)	52 (16%)	18 (6%)	3 (1%)	23.4 (16.0)	328
Crohn's Disease	0 (0%)	0 (0%)	9 (8%)	35 (32%)	35 (32%)	22 (20%)	7 (7%)	41.4 (13.8)	108
Terminal Illness	2 (2%)	9 (10%)	3 (3%)	8 (9%)	20 (21%)	38 (40%)	14 (15%)	48.7 (20.1)	94
<i>Pain</i>	0 (0%)	7 (11%)	1 (2%)	6 (9%)	16 (24%)	27 (41%)	9 (14%)	48.7 (20.1)	66
<i>Nausea/Vomiting</i>	1 (2%)	4 (9%)	2 (4%)	3 (7%)	9 (20%)	21 (47%)	5 (11%)	48.7 (20.3)	45
<i>Cachexia/Wasting</i>	1 (3%)	4 (11%)	2 (5%)	1 (3%)	3 (8%)	19 (50%)	8 (21%)	48.9 (20.3)	38
HIV/AIDS	0 (0%)	0 (0%)	0 (0%)	8 (15%)	20 (37%)	26 (48%)	0 (0%)	47.0 (9.7)	54
Tourette Syndrome	0 (0%)	11 (37%)	3 (10%)	12 (40%)	3 (10%)	1 (3%)	0 (0%)	25.3 (11.7)	30
Glaucoma	0 (0%)	0 (0%)	1 (4%)	0 (0%)	4 (17%)	11 (46%)	8 (33%)	60.4 (14.0)	24
ALS	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (9%)	12 (55%)	8 (36%)	61.5 (9.6)	22

Race and Ethnicity

Table 2.4 shows patient-reported race and ethnicity. Patients were given the option to select multiple race and ethnicity categories, so the counts reflect some patients more than once. Ninety-one patients selected more than one race/ethnicity and 95 patients declined the question. Compared to 2014 Census Bureau estimates of race/ethnicity in Minnesota, the distribution of responding members of the first program year cohort is generally similar, with a slightly higher proportion of American Indians (2.7% versus 1.9%) and lower proportion of Hispanics (2.4% versus 4.9%) and Asians (1.7% versus 5.0%).

Table 2.4. One-year cohort patient race and ethnicity compared to overall state demographics.

Race/Ethnicity	Medical Cannabis Registry	2014 Census Bureau Estimates
American Indian	42 (2.7%)	1.9%
Asian	27 (1.7%)	5.0%
Black	101 (6.5%)	6.5%
Hawaiian	3 (0.2%)	0.1%
White	1410 (90.1%)	87.5%
Hispanic	37 (2.4%)	4.9%
Other	26 (1.7%)	1.7%

Race and ethnicity estimates for Minnesota can be found at the following website:
<http://factfinder.census.gov/faces/nav/jsf/pages/index.xhtml>

Registered Caregivers and Parents/Legal Guardians

If a patient is unable to pick up their medication from a cannabis patient center or is unable to administer the medication, their certifying health care practitioner may also certify the patient's need for a designated caregiver. This allows the enrolled patient to have a caregiver who then undergoes a background check and registers with the program. Registered caregivers can then legally obtain and possess the patient's medical cannabis on their behalf. Additionally, parents or legal guardians of patients can register with the program to act as caregiver and pick up or possess medication on behalf of the patient. Table 2.5 shows the proportion within each

qualifying condition group of patients who have registered caregivers or parents or legal guardians registered to pick up medication on behalf of the patient. Patients certified for ALS, cancer, or terminal illness have the highest proportions of patients with registered caregivers (32%, 15% and 15%, respectively). Patient certified for seizure disorders or Tourette syndrome, who are also generally younger than the cohort at large, have the highest proportion of patients with registered parents or legal guardians in the program (65% and 53%, respectively). Patients with seizures or Tourette syndrome also have the highest proportion of either registered caregivers or registered parents/legal guardians. Table 2.6 shows the absolute number of registered caregivers associated with a patient in the first year cohort, reported by condition. Most patients with registered caregivers have only one caregiver able to pick up medication on their behalf (n=157); 21 patients have two caregivers and one patient has three caregivers.

Table 2.5. Proportion of patients with registered caregivers, parents or legal guardians authorized to pick up medication, or both.

CONDITION	Number of Enrolled Patients	Patients with Registered Caregiver(s)	Patients with Registered Parent(s)/Legal Guardian(s)	Patients with Registered Caregiver(s) or Parent(s)/Legal Guardian(s)
All Conditions	1660	179 (11%)	279 (17%)	430 (26%)
Cancer	466	71 (15%)	23 (5%)	92 (20%)
Terminal Illness	94	14 (15%)	10 (11%)	22 (23%)
Glaucoma	24	3 (13%)	0 (0%)	3 (13%)
HIV/AIDS	54	1 (2%)	0 (0%)	1 (2%)
Tourette Syndrome	30	2 (7%)	16 (53%)	16 (53%)
ALS	22	7 (32%)	1 (5%)	8 (36%)
Seizures	328	32 (10%)	213 (65%)	225 (69%)
Muscle Spasms	713	72 (10%)	26 (4%)	96 (13%)
Crohn's Disease	108	6 (6%)	3 (3%)	8 (7%)

Table 2.6. Count of registered caregivers associated with patients enrolled in the first program year, by qualifying condition.

Condition	Registered Caregiver Count
All Conditions	202
Cancer	83
Terminal Illness	19
Glaucoma	4
HIV/AIDS	1
Tourette Syndrome	2
ALS	7
Seizures	37
Muscle Spasms	79
Crohn's Disease	6

Geographic Distribution and Distance to Nearest Cannabis Patient Center

At the time of registration, patients provide their home address for verification of Minnesota residency. Home addresses are retained in the patient’s online registry account but are not retained in the research database; in lieu of home address, patient ZIP codes and calculated distances from each address to the nearest cannabis patient center are accessible for research purposes. The general geographic distribution of patients was examined using patient-reported ZIP codes; the first three digits of ZIP codes compose a prefix which corresponds to an approximate geographic region¹. The U.S. Postal Service assigns to each prefix labels that match

¹ <http://pe.usps.com/Archive/HTML/DMMArchive20050106/print/L002.htm>

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the major city within the region and approximate surrounding cities; these region labels are shown in Table 2.7, along with the count of patients living in the corresponding ZIP codes.

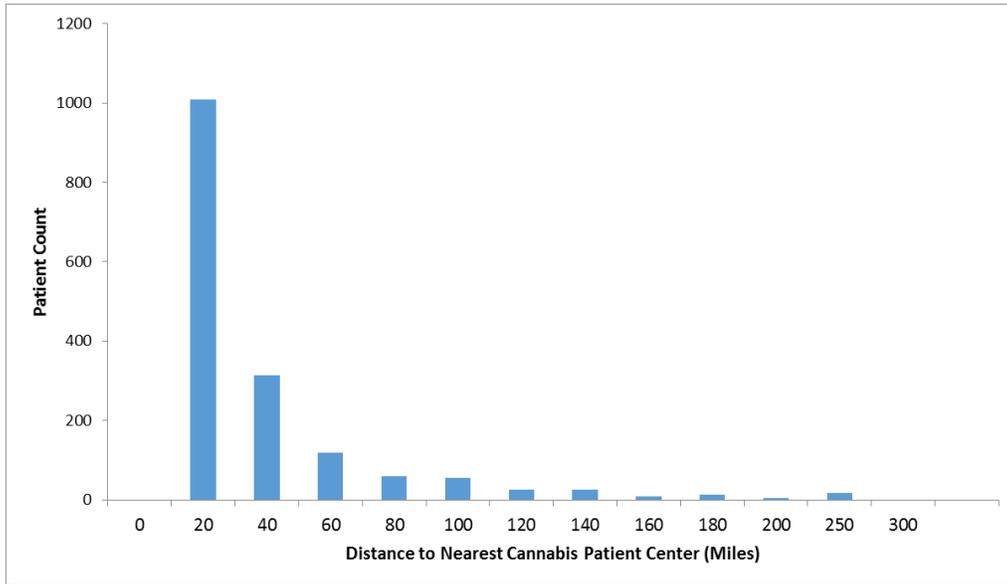
Table 2.7. Geographic distribution of patients by ZIP code prefix.

Region	ZIP Code Range	Patient Count (%)
St Paul	55000-55199	561 (34%)
Minneapolis	55300-55599	671 (40%)
Duluth	55600-55899	59 (4%)
Rochester	55900-55999	104 (6%)
Mankato	56000-56199	63 (4%)
Willmar	56200-56299	49 (3%)
St Cloud	56300-56399	80 (5%)
Brainerd	56400-56499	27 (2%)
Detroit Lakes	56500-56599	28 (2%)
Bemidji	56600-56699	11 (1%)
Grand Forks*	56700-56799	7 (0%)

Note: The Grand Forks region, corresponding to ZIP codes with a 567 prefix, refers to a region including Grand Forks, South Dakota, as well as several ZIP codes located in Minnesota near the western border. Patients living in this region reside in Minnesota.

Two medical cannabis manufacturers each operate four cannabis patient centers where patients can purchase medical cannabis following consultation with pharmacy staff at the center. Minnesota law required that one cannabis patient center be open in each of Minnesota’s eight legislative districts by July 1, 2016 (one year after the program start date). Figure 2.4 shows the distribution of calculated one-way distance from each patient’s home address to the nearest cannabis patient center location as of July 1, 2016, when all eight centers were operational. Average one-way distance is 28.9 ± 36.9 miles; median one-way distance is 15.5 miles. The majority of patients (n=1441; 86.8%) live within 60 miles of the nearest cannabis patient center.

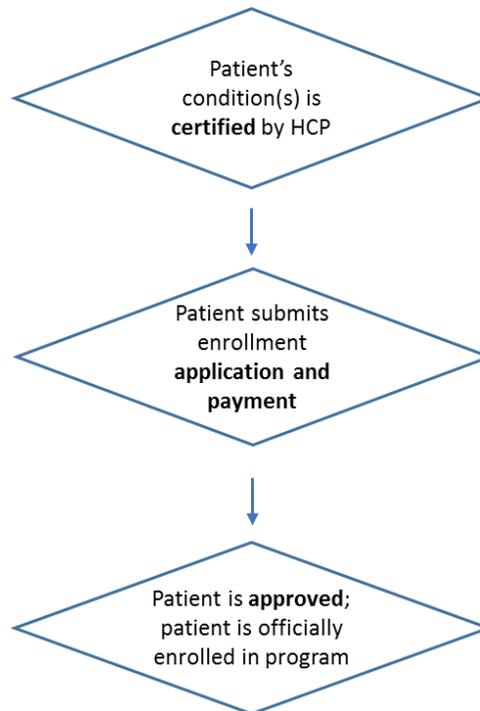
Figure 2.4. Distribution of one-way distance from patient home to nearest cannabis patient center.



From Certification to Program Approval: How Long Does it Take for Patients?

A sequential series of steps are followed in order to move patients from certification by a healthcare practitioner to their enrollment in Minnesota’s Medical Cannabis program. First, patients must have at least one medical condition that qualifies for the program and must have that condition certified by a registered health care practitioner (HCP). After their medical condition is certified, patients have 90 days to submit a complete application to enroll in the program. Patients must also submit payment to cover the annual enrollment fee along with their application materials. Once the application and enrollment fee are submitted, Office of Medical Cannabis (OMC) staff reviews and verifies all submitted materials and can approve the patient for the program. Figure 2.5 depicts the process flow from certification to program approval:

Figure 2.5. Flow chart of enrollment events.



To give current and prospective patients some idea of the time it takes to go from certification to program approval, records from patients in the first program year cohort (n = 1660) were analyzed at different time points: 1) time between certification to program approval, 2) time between certification to enrollment payment, and 3) time between enrollment payment and program approval.

Time from Certification to Program Approval

Just over half of all patients (54.7%) in the cohort (n = 1660) were approved/enrolled in the program within 3 days of having their condition(s) certified. Close to 90% (1484 out of 1660 patients) were enrolled in the program within a month of being certified.

Time from Certification to Annual Enrollment Fee Payment

Records of enrollment fee payments were unavailable for patients who did not make an electronic payment; therefore, calculations of time between certification and enrollment fee payment was restricted to 1579 patients (95.1% of patients in the cohort represented) who paid the enrollment fee electronically. Of these patients, 57.2% of them (n = 903) submitted payment within 1 day of getting their qualifying condition(s) certified by their HCP. More than 90% of patients (n = 1452) submitted payment within one month of certification.

Time from Annual Enrollment Fee Payment and Program Approval

Records of enrollment fee payments were not available for all patients in the cohort; therefore, calculations of time between enrollment fee payment and program approval was restricted to 1579 patients (95.1% of patients in the cohort represented). Of these patients, 72.7% of them (n = 1148) were approved for the program (officially enrolled in the program) within a day of submitting their annual enrollment fees. Close to all patients (99.3%) were enrolled in the program within a month of submitting their annual enrollment fees. The small proportion of patients who do not get approved within a month of their fee submission generally reflects patients who submitted inadequate or incomplete information during the enrollment submission process (meaning that the Office of Medical Cannabis is waiting for additional information to approve them for the program).

From Certification to Program Approval: Conclusions

Just over half of all patients in the cohort were officially enrolled in the program within three days of being certified. Within a week of certification, 70% of patients were enrolled in the program. This suggests that the majority of patients move relatively quickly from certification to enrollment in the program.

When breaking down the process flow between certification and program approval, it typically took longer for patients to move from certification to paying the enrollment fee than it did from their paying the enrollment fee to getting approved. This generally reflects the nature of the process flow going from certification to paying the enrollment fee: after patients are certified, the patient must self-initiate and complete the submission of all application materials along with payment (involves variable amounts of time to gather all materials and to ensure sufficient funds to make fee payment). This is in contrast to the step between enrollment fee payment and getting approved for the program: patient has submitted all materials and payment by this

point and – unless they are directed otherwise by OMC staff – will get approved for the program in the order their materials were received in the queue.

Re-Enrollment

The Minnesota medical cannabis program requires by statute that once a patient becomes certified as having a qualifying condition and enrolled in the program, the patient's enrollment lasts for one year; therefore each year a patient must be re-certified as having at least one qualifying condition and must re-enroll in the program and pay an annual enrollment fee. If a patient is not re-certified as having a qualifying condition and does not re-enroll in the program by the anniversary date of the most recent enrollment, their account is deactivated and they are no longer able to purchase medical cannabis from a cannabis patient center or retain the protections of the program. To investigate the rate at which enrolled patients who approach their expiration dates re-enroll in the program, patients who enrolled in the program during the first program month (including those who were approved early, prior to the program start in July 2015) were examined. A total of 253 patients were enrolled in the first program month; these patients' enrollments expired in July 2016. Re-enrollment activity for these patients was examined six months following expiration of the first enrollment year. Within six months following the expiration of the first year of enrollment, 115 (45%) among these patients re-enrolled in the program. Of the remaining 138 patients who did not re-enroll during this period, 24 patients (17%) died within 18 months of initial enrollment. Additionally, patients can re-enroll at any time following expiration, and some patients who did not re-enroll immediately may do so at a later time.

Most patients who re-enrolled within six months of expiration did so prior to expiration (44%) or within the first month after enrollment expiration (40%). Only 3% of these patients re-enrolled beyond three months post expiration. Timing of re-enrollment for patients who initially enrolled during the first program month are shown in Table 2.8.

Table 2.8. Timing of program re-enrollment for patients enrolled in the first program month.

Time Re-Enrollment Occurred	Patient Count (%)
Prior to Expiration	51 (44%)
1st Month After Expiration	46 (40%)
2nd Month After Expiration	0 (0%)
3rd Month After Expiration	15 (13%)
4th Month After Expiration	1 (1%)
5th Month After Expiration	2 (2%)
6th Month After Expiration	0 (0%)
<i>Total Count of Patients Re-enrolled Within 6 Months of Annual Expiration Date</i>	<i>115</i>

Note: Among the 253 patients who enrolled in the program in July 2015, 115 (45%) re-enrolled within six months of expiration. Percentages are based on a total number of re-enrollments within this period (n=115).

At the time of enrollment expiration, a patient can allow their enrollment to lapse without any action or communication with the Office of Medical Cannabis. Currently OMC does not collect information systematically on why patients chose to either re-enroll or let their current enrollment expire. However, some insight into program discontinuation is available from a Continued Use survey, which asks patients who have not purchased medical cannabis for 60 days whether they have decided to stop the treatment, whether they received any benefits from the treatment, and what their reasons are for either stopping or pausing the treatment. Early results looking at patients who purchased medical cannabis within the first three program months but discontinued purchasing for 60 days showed that 62% (n=10) of patients who indicated they planned to stop using medical cannabis (n=16) found little or no benefit from the treatment. Among 59 patients who indicated they were unsure of whether they would continue or that they intended to continue the treatment, 35 (73%) cited cost as a barrier to continuing. These results do not directly answer the question of why some patients do not re-enroll but give some indication of potential reasons for doing so. (For methodology and preliminary results from the Continued Use survey, see [“Early Results of Office of Medical Cannabis Surveys: May 2016”](#) on the [Office of Medical Cannabis](#) website).

3. Health Care Practitioners Registered in the First Program Year

The Minnesota Medical Cannabis program outlines a set of qualifying medical conditions which make a patient eligible for enrollment in the program. By Minnesota statute, a patient must be certified by a Minnesota-licensed physician, physician assistant (PA), or advanced practice registered nurse (APRN) as having one or more of the qualifying conditions. A Minnesota practitioner with appropriate credentials must first register with the Minnesota Medical Cannabis program before they can certify patients for the program: practitioners complete a short online form with their name and clinic information to register. Office of Medical Cannabis staff verify the provider's entered information and their Drug Enforcement Agency (DEA) license prior to approving the practitioner to certify patients. This chapter will describe the certifying healthcare practitioners who registered in the first program year.

Healthcare Practitioner Count, Age and Gender

From July 2015- June 2016, 577 healthcare practitioners licensed in Minnesota registered in the medical cannabis program, including 473 physicians (82%), 77 APRNs (13%) and 27 PAs (5%). Table 3.1 shows the breakdown of healthcare practitioner (HCP) type, gender and average age, based on publicly available data from the Boards of Medical Practice and Nursing. Physicians registered in the program were predominantly male (72%) and were generally older than registered APRNs and PAs, who were predominantly female (88% and 78%, respectively).

Figure 3.1. Count of registered healthcare practitioners during the first program year.

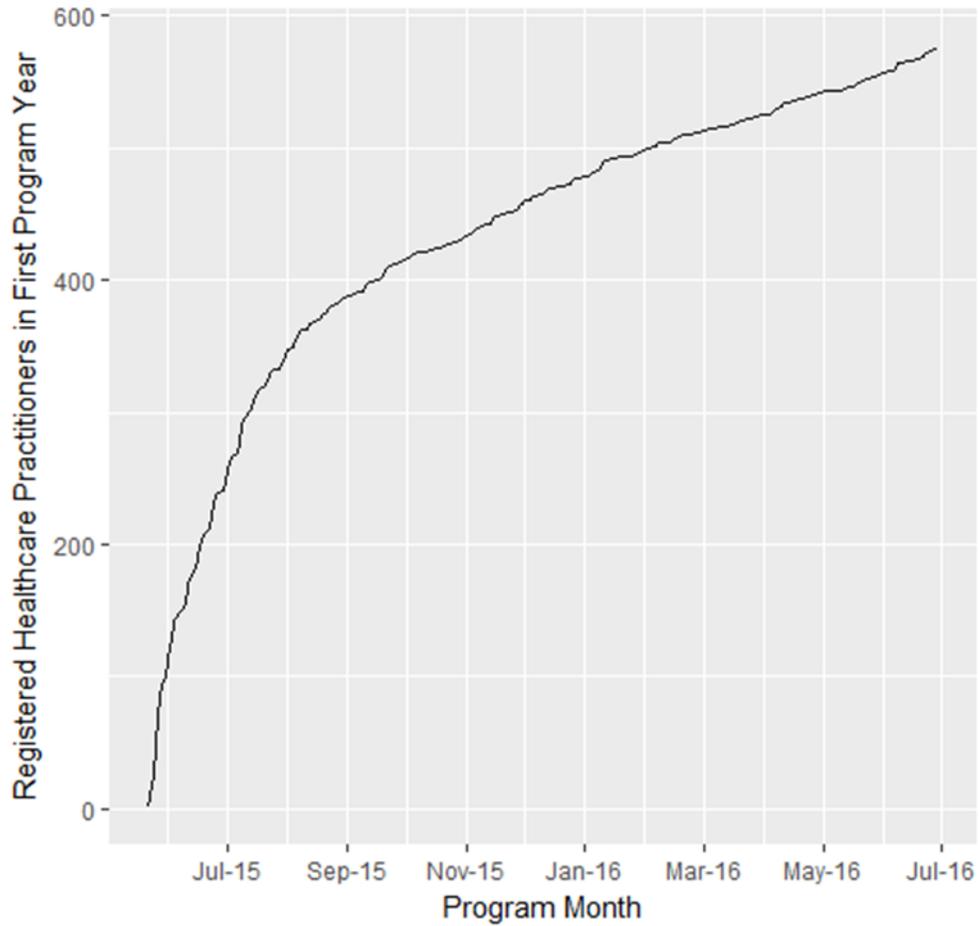


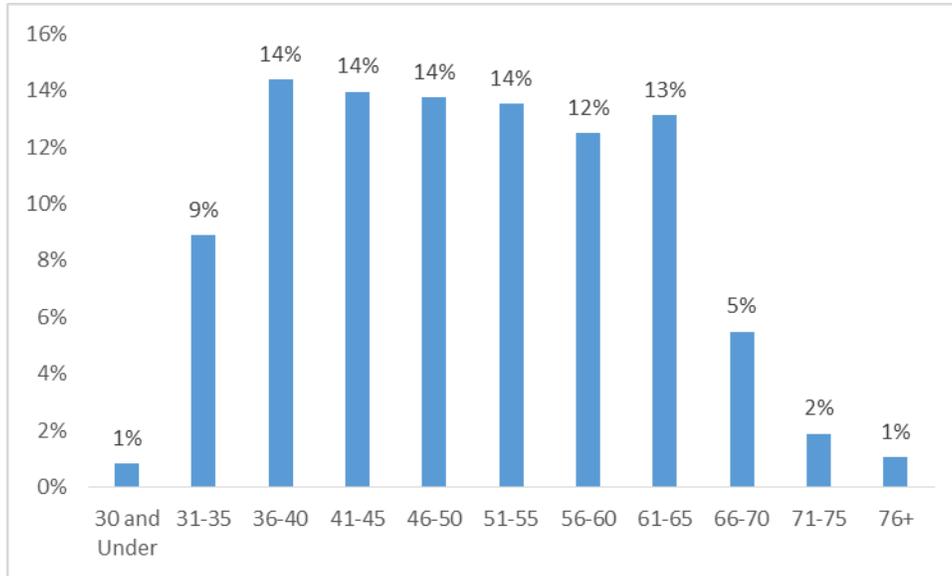
Table 3.1. Healthcare practitioner by type, with gender and average age.

HCP TYPE	N	%	MALE: N (%)	MEAN AGE (SD)
Physician	473	82%	341 (72%)	50.3 (11.3)
APRN	77	13%	9 (12%)	47.0 (9.4)
PA	27	5%	6 (22%)	39.9 (9.5)
Total	577	100%	356 (62%)	49.4 (11.2)

Note: Age data was unavailable for 17 APRNs and three physicians.

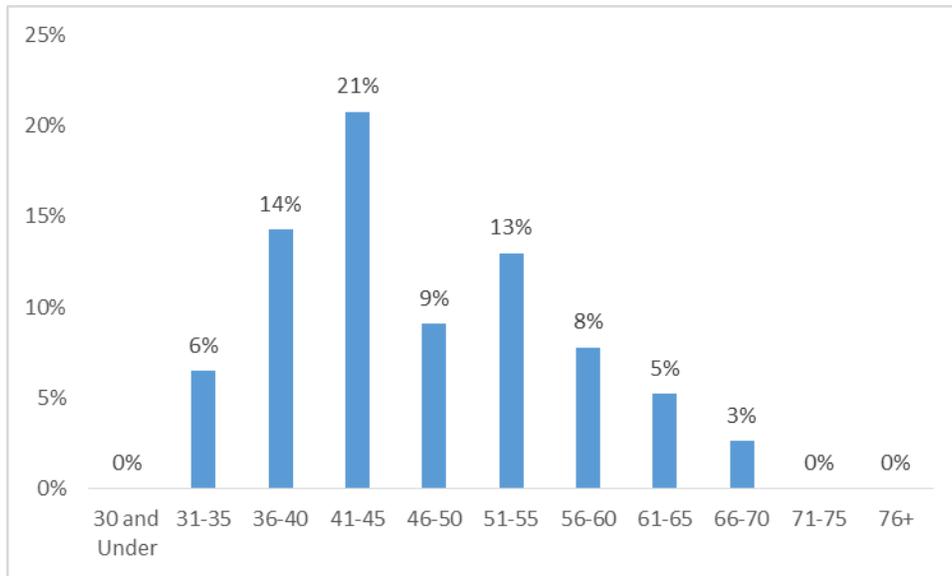
More detailed representations of age distribution among registered physicians, PAs and APRNs are available in Figures 3.2-3.4. Figure 3.2 shows the age distribution in 5 year increments of physicians enrolled in the first program year; most physicians fall between ages 36-65 years (81%) with relatively even distribution of numbers across this range. Figure 3.3 shows the age distribution for APRNs; 51% of APRNs are 50 years or under. Figure 3.4 shows the age distribution for PAs registered in the program; most PAs fall between ages 31-45 (78%).

Figure 3.2. Age distribution of physicians registered in the medical cannabis program (n=473).



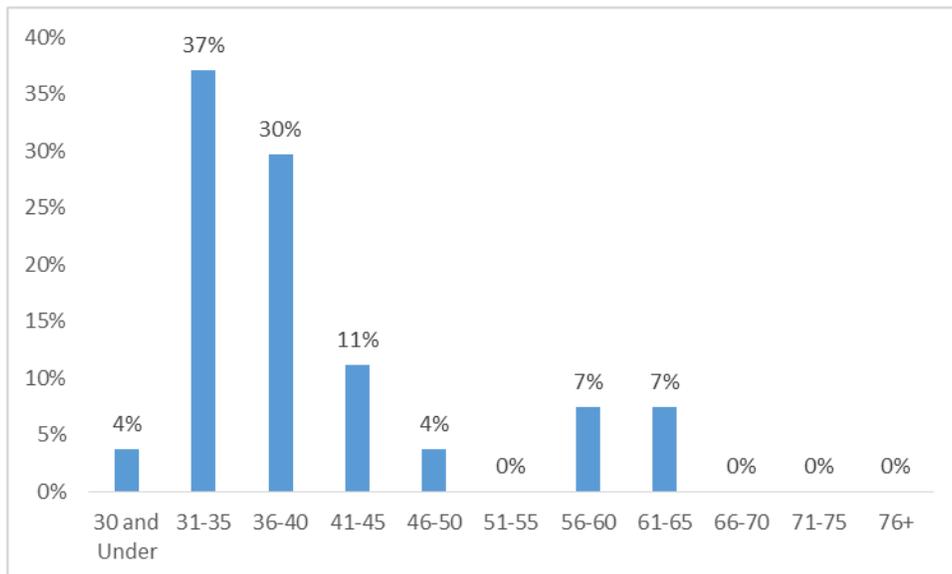
Note: Age data was not publicly available for three physicians registered in the first program year.

Figure 3.3. Age distribution of advanced practice registered nurses registered in the medical cannabis program (n=77).



Note: Age data was not publicly available for 17 APRNs registered in the first program year.

Figure 3.4. Age distribution of physician assistants registered in the medical cannabis program (n=27).



Registered Physician Specialties and Licensures

The Minnesota Board of Medical Practice lists information on Minnesota-licensed physicians and physician assistants. Included is self-reported “Area of Specialty” information indicating a physician’s (or physician assistant’s) certifications from the American Board of Medical Specialties or American Osteopathic Specialty Boards. While physician assistant specialty information is infrequently provided, physicians often list certifications in more than one area of specialty. For example, physicians practicing as oncologists may list certifications in the areas of Internal Medicine, Hematology, and Medical Oncology. A variety of specialties were represented among physicians registered in the first program year, including subspecialties of neurology (neurology with special qualifications in child neurology, clinical neurophysiology, and epilepsy), pediatrics (pediatric hematology-oncology) and internal medicine or family medicine (gastroenterology, geriatric medicine, hospice and palliative medicine, sports medicine, nephrology, and infectious disease). Specialties including ophthalmology, dermatology, radiology and surgery were also represented. In cases where a physician listed an area of specialty and subspecialty, such as Internal Medicine and Gastroenterology, the subspecialty was chosen to represent the physician’s practice (in this case, Gastroenterology). Table 3.2 shows the distribution of physician specialties; each physician is represented only once. Two physicians who are licensed in Minnesota and registered in the program do not have any listed specialties with the Board of Medical Practice; they are therefore excluded from Table 3.2. The most common specialty category for physicians registered in the first program year was primary care (38%), which included internal medicine (13%), family medicine (23%) and pediatrics (2%). Physicians with specialization in oncology (17%) and neurology (14%) were also common.

Table 3.2. Registered physician specialty categories.

Registered Physician Specialties	N (%)
Primary Care	179 (38%)
<i>Internal Medicine</i>	<i>61 (13%)</i>
<i>Family Medicine</i>	<i>109 (23%)</i>
<i>Pediatrics</i>	<i>8 (2%)</i>
Oncology	81 (17%)
Neurology	65 (14%)
Pediatric Specialty	29 (6%)
Hospice/Palliative Medicine	25 (5%)
Physical Medicine and Rehabilitation	21 (4%)
Gastroenterology	11 (2%)
Psychiatry	10 (2%)
Ophthalmology	9 (2%)
Surgery	8 (2%)
Infectious Disease	6 (1%)
Radiology/Radiation Oncology	5 (1%)
Pain Medicine	5 (1%)
Nephrology	3 (1%)
Geriatric Medicine	3 (1%)
Emergency Medicine	2 (0%)
Rheumatology	2 (0%)

Obstetrics and Gynecology	2 (0%)
Sports Medicine	2 (0%)
Anesthesiology	2 (0%)
Dermatology	1 (0%)
Public Health and Preventive Medicine	1 (0%)
Pulmonary Disease	1 (0%)
Sleep Medicine	1 (0%)

Advanced Practice Registered Nurse Licensures

Advanced practice RNs include licensed Clinical Nurse Specialists (CNS), Certified Registered Nurse Anesthetists (CRNA), Certified Nurse-Midwives (CNM) or Certified Nurse Practitioners (CNP). Among the 77 APRNs who registered in the first program year, 75 held CNP certification, 1 held CNS certification, and 1 held both CNP and CNS certifications.

Summary

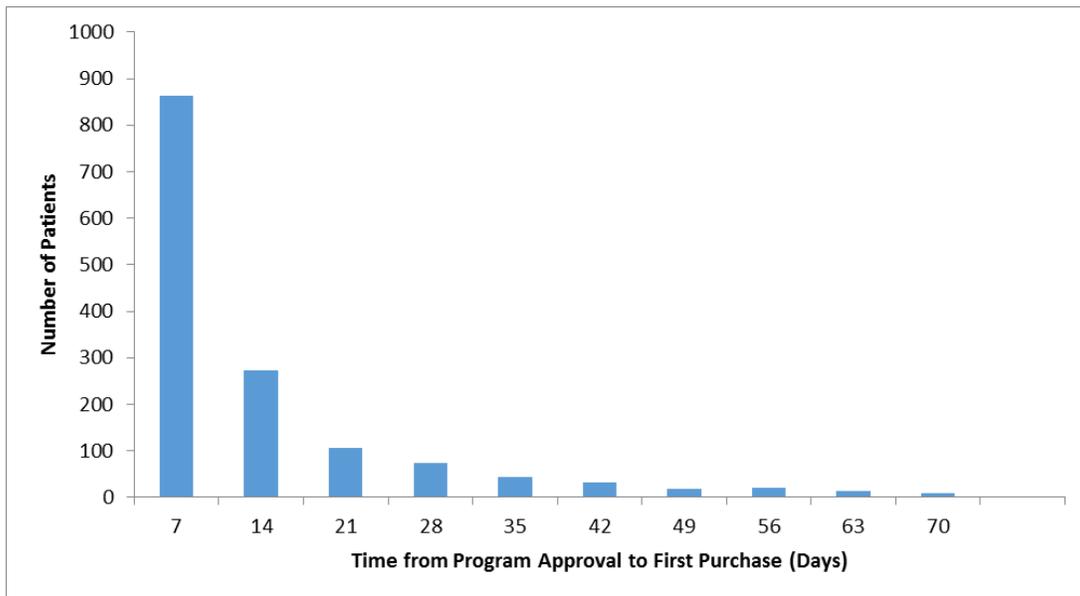
In the first year of the Minnesota Medical Cannabis program, 577 licensed healthcare practitioners registered as certifying providers with the program, predominantly physicians (82%). There were age and gender differences across the HCP types; physicians tended to be older and male; PAs and APRNs tended to be younger and female. Physician licensure information showed that physicians from a diversity of clinical practices are involved in certifying patients for the medical cannabis program, but the majority of these providers are primary care providers or specialties that typically manage patients with the Minnesota program’s qualifying conditions (i.e. severe muscle spasms, seizure disorders, Tourette syndrome and ALS are typically managed by neurologists; cancer is often managed by oncologists).

4. Frequency and Duration of Medical Cannabis Purchases

Time from Program Approval to First Medical Cannabis Purchase

Once a patient is approved for the medical cannabis program, the patient and/or their registered caregiver(s) or parent(s)/legal guardian(s) can visit any of the eight cannabis patient centers and purchase medical cannabis. Figure 4.1 shows the distribution of time from program approval to first medical cannabis purchase for patients enrolled during the first program year who purchased medical cannabis before December 31, 2016 (n=1528). Many patients (n=196; 13%) made a first purchase within one day of program approval; over half (n=864; 57%) made a first purchase within seven days and most patients (n=1137; 74%) made a first purchase within 14 days of program approval.

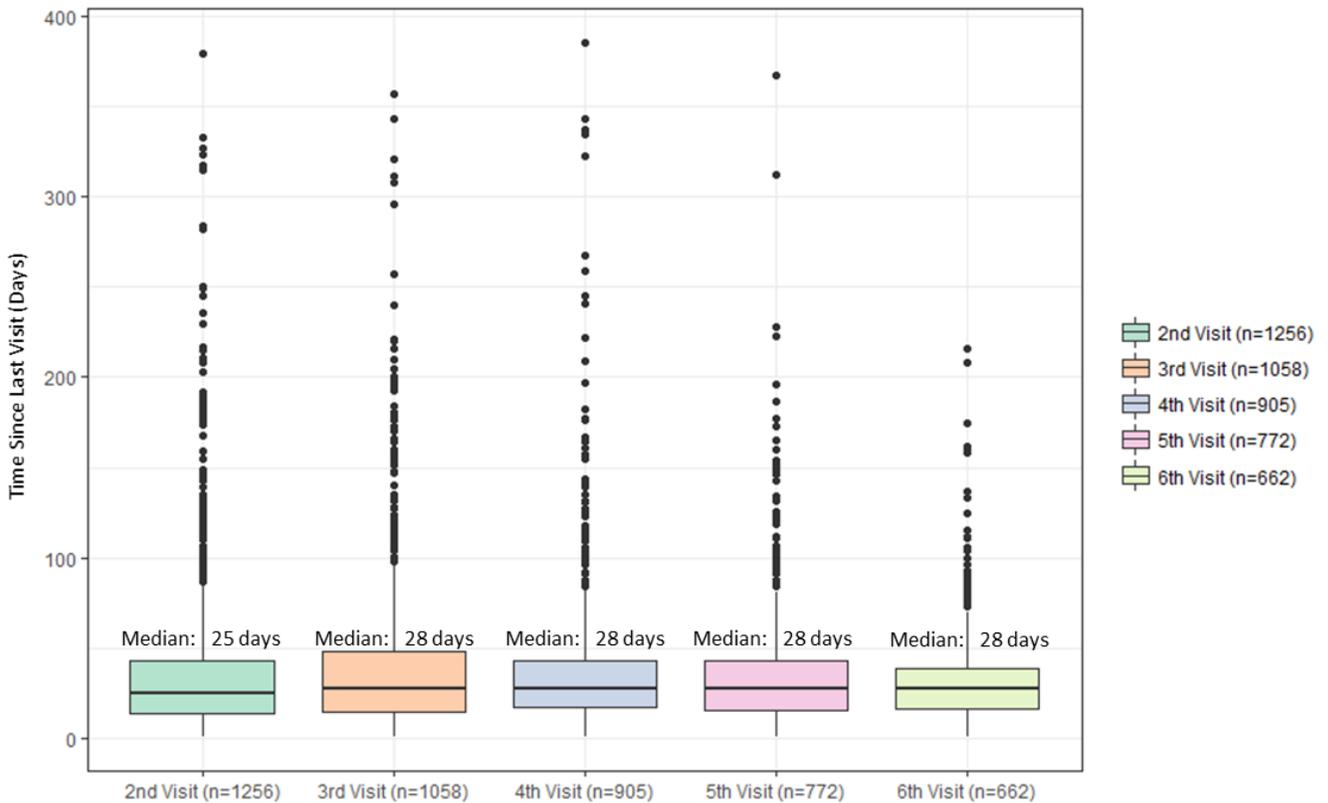
Figure 4.1. Time from patient approval to first medical cannabis purchase.



Time Between Purchases

According to Minnesota statute, patients can purchase up to a 30-day supply of medicine at a cannabis patient center. However, visits to a cannabis patient center vary from 30-day intervals for several reasons. Figure 4.2 shows the intervals between purchases for patients from the one-year cohort with at least two purchases (n=1256). Patients must purchase medical cannabis with cash and many patients report that the medicine's cost is prohibitive; for these reasons, patients may purchase smaller quantities than a month's supply and visit cannabis patient centers more frequently than once a month. On the other hand, many patient responses to the Continued Use Survey (see ["Early Results of Office of Medical Cannabis Surveys: May 2016"](#) on the [Office of Medical Cannabis](#) website) indicated a quantity of medicine intended to be a 30-day supply lasted longer than 30 days, or the patient chose to use the medicine sparingly as a cost-saving measure and therefore the supply lasted longer than anticipated. However, the median times between visits for the first consecutive six visits were close to the expected interval of one month (median time since last visit: 25, 28, 28, 28, and 28 days for the second, third, fourth, fifth and sixth visits, respectively).

Figure 4.2. Time between visits for patients with two or more visits from July 2015-December 2016.



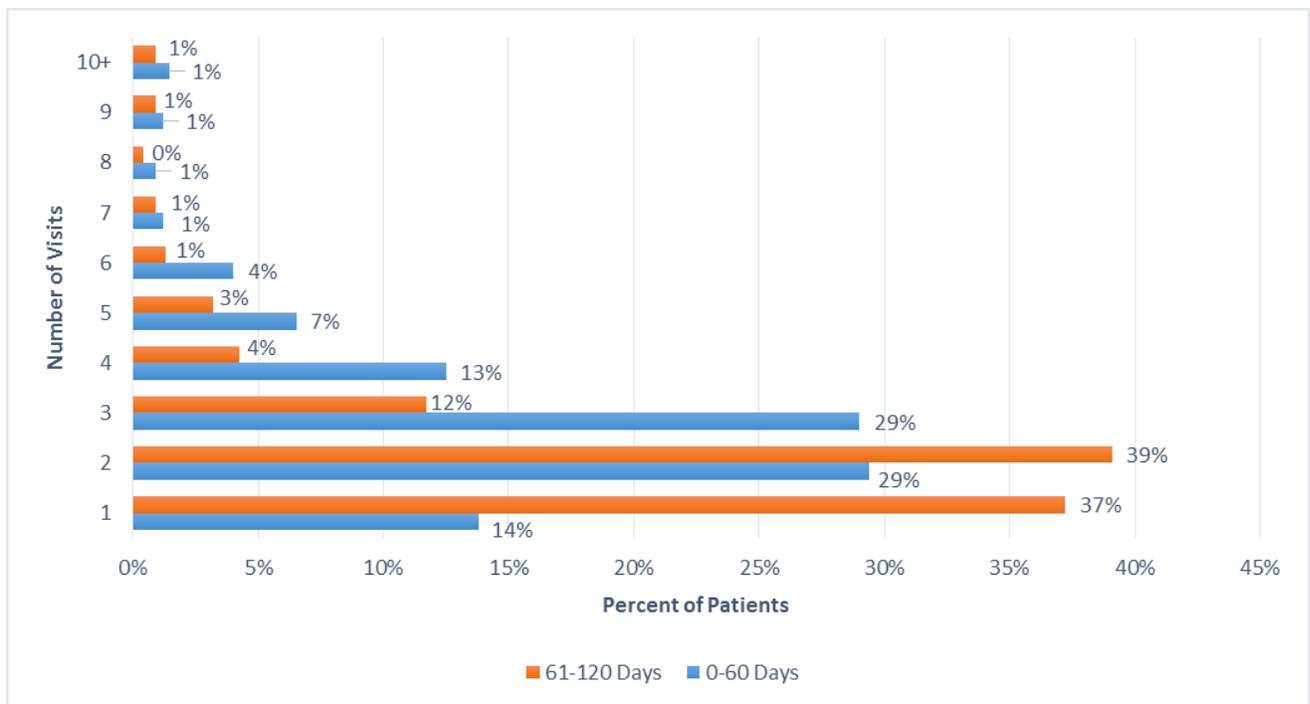
Note on boxplots: upper and lower hinges for each boxplot correspond to the 75th and 25th percentiles of each distribution, respectively. The upper and lower whiskers extend to the highest and lowest values that are within 1.5 x the interquartile range from the upper and lower hinges, respectively. Data beyond the whiskers, plotted as individual points, are outliers.

Purchasing Activity in First Four Months of Program Participation

Patients beginning medical cannabis treatment often try different types of products with varying ratios of THC:CBD and routes of administration to achieve optimal symptom management; therefore patients may be more likely to make more visits to cannabis patient centers at the beginning of treatment and fewer visits in later times once the patient’s regimen had been established. As seen in Figure 4.2, frequency of visits (represented as time between consecutive visits) varies widely across patients. To compare purchasing activity in the first two months versus the second two months of program activity, the number of visits for each patient with continuous enrollment was examined in the first and second 60 days of program activity (day 0 defined as the date of first medical cannabis purchase). Patients who made no

purchases between days 61 and 120 or beyond day 120 were excluded to eliminate patients who had atypical purchasing activity or quit the program during this time window. Figure 4.3 shows the distribution of number of visits per patient which occurred in the first and second 60 days of program activity (n=752). During the first 60 days of program activity, median number of visits was 3 and 543 of 752 patients in this group (72%) made three or fewer purchases. During days 61-120 of program activity, median number of visits was 2 and 662 of 752 patients (88%) made three purchases or less. While the distributions of purchasing activity in the first 60 days and second 60 days is roughly similar, they indicate that purchasing activity is slightly greater during the first 60 days of program activity.

Figure 4.3. Number of visits in first 60 days and second 60 days of program activity, for patients with one or more purchases in both 60 day intervals.

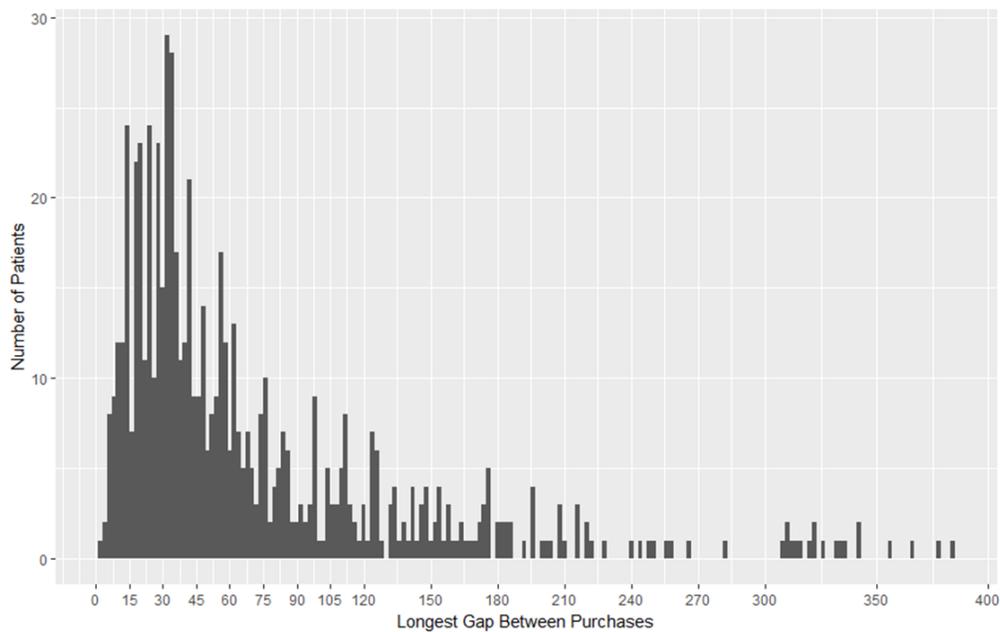


Patients Who Stopped Purchasing Medical Cannabis

Since patients make an annual payment to be enrolled in the medical cannabis program, if they decide at some point during the following year to discontinue medical cannabis treatment, it is unlikely they will request to be withdrawn from the program, as there is no financial incentive to do so. Therefore, to understand discontinuation in the program, a functional definition was created based on purchasing patterns. For each patient in the one year cohort enrolled with a first purchase prior to December 31, 2015 and making at least two purchases before December 31, 2016 (n=669), the longest gap between consecutive purchases from July 2015-December 2016 is shown in Figure 4.4; median longest gap in this group was 47 days. Among these

patients, 546 (82%) had a longest gap between purchases of 120 days or less; 616 (92%) had a longest gap between purchases of 180 days or less. Median longest gap for each patient is significantly longer than median time between visits for patient's first six visits; this suggests that there may be a great deal of variability within a patient's inter-visit times. Early patient responses to the Continued Use survey point to factors which may impact purchasing frequency: unexpectedly low rate of product usage, cost-motivated reduction or temporary cessation of product usage, unrelated medical treatment changes which interfered with cannabis usage, or out-of-state travel.

Figure 4.4. Distribution of longest gap between visits per patient, July 2015-December 2016.



Since most patients (92%) enrolled and purchasing within the first six program months who made two or more purchases by December 31, 2016 had no inter-visit gaps longer than 180 days, program discontinuation was defined for this analysis as ceasing purchasing activity for six months or longer during the period included in this analysis (July 2015-December 2016). This definition was applied to all patients enrolled in the first six program months who made at least one purchase (n=774) to find the proportion of patients (regardless of duration enrolled in the program) who did not make any purchases for at least six months, through the end of 2016. Of these 774 patients making at least one medical cannabis purchase, 398 patients (51%) made no purchases for at least six months, as of December 2016. Based on the distribution of longest gaps between purchases in this subset of the one-year cohort, it is likely that this proportion is

a rough estimate of the proportion of patients who quit the program within 18 months after trying medical cannabis.

Using a six month window with no purchases as a surrogate for program discontinuation has limitations. For example, our analysis did not account for duration of enrollment and any effect it may have on purchasing patterns. However, it gives an approximation of patients who abandon medical cannabis treatment and roughly aligns with the re-enrollment rate of 45% in patients enrolled in the first program month (see “Re-Enrollment” in Chapter 2: Description of Patients and Designated Caregivers).

Frequency and Duration of Medical Cannabis Purchases: Conclusions

Most patients make their first medical cannabis purchase within 14 days of program approval. Subsequent purchases often follow a roughly monthly periodicity, with median inter-visit gap at 25 days for the gap between the first and second visit and 28 days for the next four inter-visit gaps. Additionally, patients tend to make purchases slightly more frequently in the first 60 days of program activity compared to the second 60 days of program activity (median number of visits is 3 from 0-60 days and 2 from 61-120 days). Finally, most patients (92%) do not have an inter-visit gap longer than 180 days; using 6 months or more of no purchasing activity as a surrogate for program discontinuation, 51% of patients who enrolled and made a purchase within the first six months of the program ceased purchasing medical cannabis as of December 31, 2016.

5. Medical Cannabis Use Patterns

Medical cannabis purchasing records were extracted from the registry in early March 2017 for patients enrolled in the 1st program year. From this data, all transactions that occurred within a patient's first enrollment year were retained. For those patients whose first enrollment year had not yet ended at the time of data extraction, all purchasing transactions were retained. This resulted in a dataset with the following:

- 10,898 purchasing transactions consisting of:
- 16,238 products within these transactions (37.9% of all purchasing transactions consisted of two or more products), which
- Represented 1529 patients (92.1% of the first program year cohort).

For analytical purposes, all 16,238 product transactions were classified according to the ratio of delta-9-tetrahydrocannabinol (THC) to cannabidiol (CBD) found in the medical cannabis products. Products ranged from containing very high THC to CBD content to those with very high CBD to THC, as well as everything in between (products with relatively balanced amounts of THC and CBD). For definitions on THC:CBD ratio classifications, see Box 5.1.

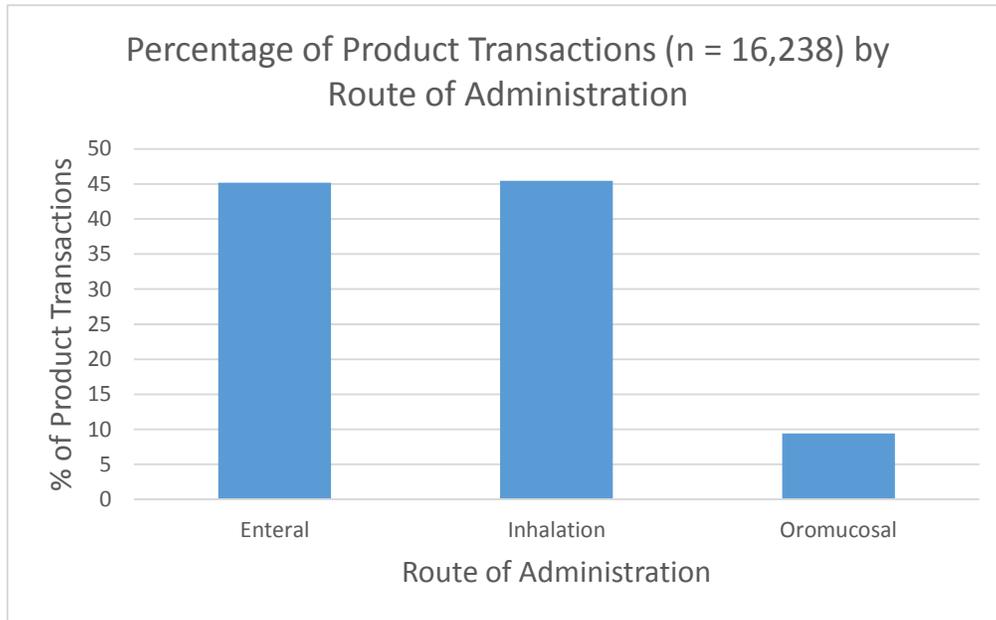
Box 5.1. Definitions to classify medical cannabis products by THC:CBD ratios.

Product Classifications Based on THC to CBD content:

- **Very High THC to CBD** = 100:1 or higher
- **High THC to CBD** = >4:1 up to 99:1
- **Balanced** = 1:1 up to 4:1
- **High CBD to THC** = \geq 1:1 up to 99:1
- **Very High CBD to THC** = 100:1 or higher

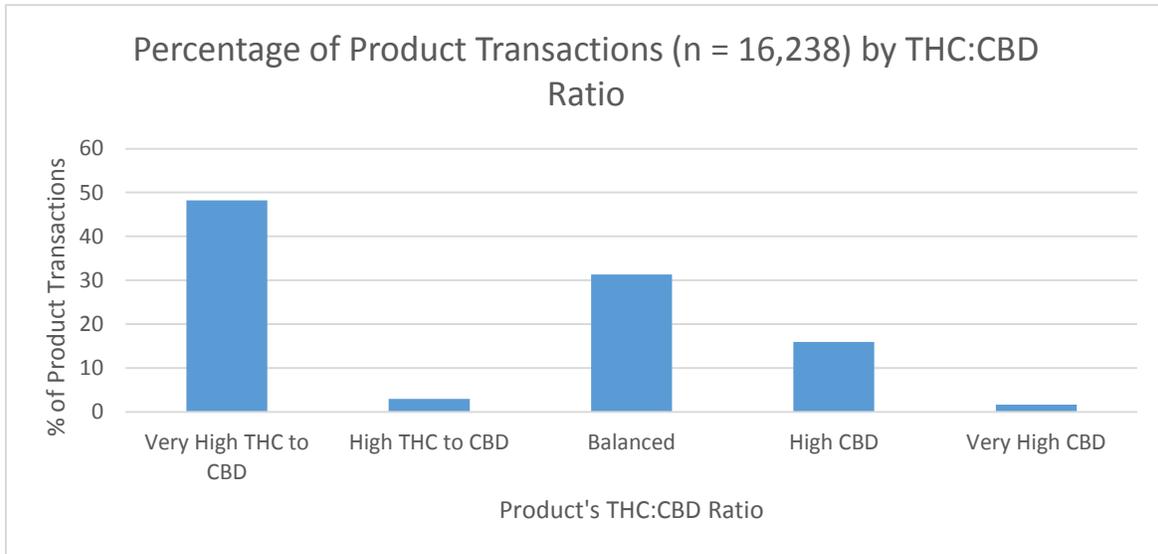
Products purchased for enteral administration (swallowed – includes capsules and oral solutions) and inhalation (vaporized oil) represented the majority of the products purchased (90.6% of all product transactions) with significantly fewer products purchased for oromucosal absorption (oil absorbed through cheek; 9.4% of all product transactions). In fact, products for enteral administration and inhalation were roughly equally purchased by patients, respectively representing 45.2% (n = 7333) and 45.4% (n = 7376) of all products dispensed. See Figure 5.1.

Figure 5.1. Purchasing transactions categorized by the product’s intended route of administration (out of 16,238 products dispensed).



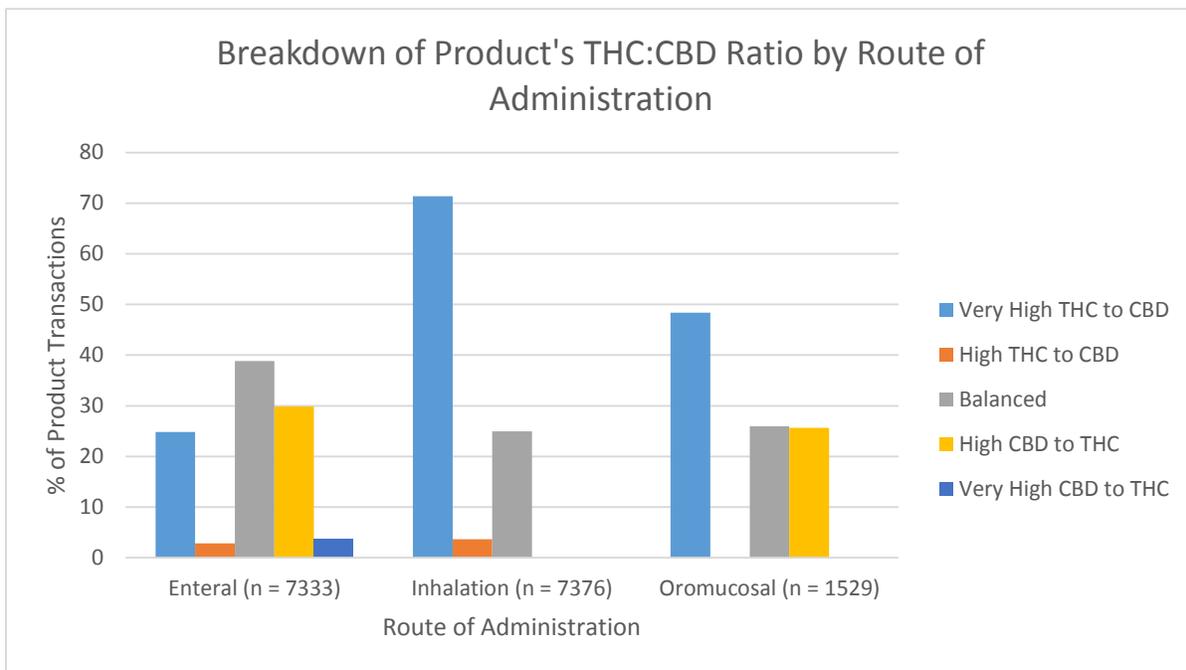
When products were classified by the ratio of THC to CBD present in the product, the following patterns emerged. Firstly, 48.2% of all product transactions were for products with very high THC amounts compared to CBD (hundreds to one). Balanced products (roughly equal amounts of THC to CBD) represented the next biggest group of products purchased, representing 31.3% of products dispensed. This was followed by high CBD to THC products which represented 15.9% of all product transactions. See Figure 5.2.

Figure 5.2. Product transactions represented by the THC to CBD ratio available in the product.



Product transactions were also examined by the products' THC:CBD ratios as a function of their routes of administration (see Figure 5.3). Of all product transactions intended for enteral administration, close to 39% of them were for products with relatively balanced THC:CBD ratios followed by products with high CBD:THC (29.9%) and very high THC:CBD products (24.8%). Product transactions for inhalation predominately had very high THC to CBD (71.4%). Lastly, close to half (48.4%) of all oromucosal product transactions were for very high THC:CBD products, with roughly a quarter each constituting balanced and high CBD to THC products (respectively 26.0% and 25.6%).

Figure 5.3. A percentage breakdown of product transactions by the THC:CBD product ratio types as a function of route of administration.



Most Frequently Purchased Product(s)

Examining purchasing history across all patients is very complex. For example, patients may experiment with different products as they explore what works best for them, and some may establish a pattern of using more than one product. Additionally, those using more than one product do not always purchase all of those products at each purchasing transaction. As a first approach to assessing routine use of products, we report here the product(s) most frequently purchased by each patient. Table 5.1 shows the product(s) that were identified as the most frequently purchased by patients (indicated by “X”), as well as the percentage of patients it represents from the 1529 patients included in this analysis. Additionally, the table displays the average daily THC and CBD dose across patients for the product(s) purchased most frequently based on THC/CBD content information (provided by the medical cannabis manufacturers) as well as pharmacist-entered information regarding the length of time the product supply should last. Omitted from display in Table 5.1 are cases where two or less people had the same combination of most frequently purchased product(s)—this was done for ease of interpretation, as some of those cases seemed to be indicative of a wider range of experimentation across multiple products and/or indicative of patients with a shorter purchasing history.

Table 5.1 shows that roughly 72% of all patients most frequently purchased a single product that falls under 1) a specific THC:CBD ratio and 2) is intended for a particular route of administration (note the rows that have a single “X” in Table 5.1). Roughly a quarter of all patients most frequently purchased a very high THC to CBD product intended for vaporization followed by relatively similar numbers of patients most frequently purchasing a single, balanced-enteral product or a single, high CBD:THC-enteral product (respectively 12.6% and 13.7%). For patients most frequently purchasing two or more products an equal number of times, the most common combination was for an enteral-balanced product and an inhaled-very high THC:CBD product, accounting for 3% of all patients.

While the subsequent portions of this section will be devoted to stratifying routine product use by qualifying condition, the following statement should be made: the method for determining routine product use in this report (most frequently purchased) is relatively simple and, therefore, poses limitations for understanding the complexities in medication usage. Future endeavors will include a further discussion and potential refinement in methodology to better capture medical cannabis use in program participants

Table 5.1. Product(s) most frequently purchased by each patient (out of 1529 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 1529 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
					X										25.4 (389)	83.2 mg / 0.4 mg
			X												13.7 (209)	8.5 mg / 174.2 mg
		X													12.6 (193)	38.8 mg / 29.7 mg
							X								5.8 (88)	39.5 mg / 17.2 mg
X															5.0 (77)	70.8 mg / 0.3 mg
										X					4.3 (66)	39.8 mg / 0.2 mg
		X			X										3.0 (46)	99.2 mg / 47.5 mg
					X		X								2.7 (41)	84.9 mg / 14.0 mg
X					X										2.4 (36)	69.5 mg / 0.4 mg
												X			2.2 (34)	46.3 mg / 33.0 mg
		X					X								2.1 (32)	44.0 mg / 26.5 mg
X		X													1.4 (21)	48.0 mg / 15.0 mg
				X											1.3 (20)	6.9 mg / 1225.3 mg
		X								X					1.2 (19)	82.5 mg / 30.8 mg
					X					X					1.2 (18)	91.3 mg / 0.5 mg
													X		1.2 (18)	2.9 mg / 121.6 mg
X										X					1.0 (15)	46.8 mg / 0.2 mg
X		X					X								0.9 (14)	65.6 mg / 18.2 mg
X		X			X		X								0.7 (11)	164.8 mg / 54.1 mg
X		X			X										0.7 (10)	137.0 mg / 21.9 mg
		X			X		X								0.6 (9)	838.8 mg / 211.5 mg
							X								0.6 (9)	963.5 mg / 56.7 mg
		X	X												0.5 (8)	18.4 mg / 121.9 mg
X					X					X					0.5 (7)	119.6 mg / 0.6 mg
	X														0.5 (7)	873.5 mg / 19.2 mg
		X	X				X								0.4 (6)	37.0 mg / 105.6 mg
			X	X											0.3 (5)	10.9 mg / 539.0 mg
			X		X										0.3 (5)	56.8 mg / 224.2 mg
			X				X								0.3 (5)	66.7 mg / 663.6 mg
					X	X									0.3 (5)	205.7 mg / 8.8 mg
										X		X			0.3 (5)	46.6 mg / 10.4 mg
		X										X			0.3 (4)	63.9 mg / 45.8 mg
			X							X					0.3 (4)	32.3 mg / 78.8 mg

MINNESOTA MEDICAL CANNABIS PROGRAM: PATIENT EXPERIENCES FROM THE FIRST PROGRAM YEAR

Table 5.1 Continued. Product(s) most frequently purchased by each patient (out of 1529 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 1529 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
X		X	X												0.2 (3)	110.4 mg / 125.2 mg
X		X								X					0.2 (3)	54.1 mg / 8.7 mg
X					X		X								0.2 (3)	122.7 mg / 25.1 mg
	X	X			X										0.2 (3)	94.4 mg / 11.3 mg
							X					X			0.2 (3)	52.2 mg / 23.4 mg
							X						X		0.2 (3)	30.5 mg / 133.2 mg
												X	X		0.2 (3)	31.5 mg / 134.4 mg

Severe and Persistent Muscle Spasm Patients

Of the 1529 patients represented in this analysis, 44.3% (677) of them were certified as having Severe and Persistent Muscle Spasms, including those Characteristic of Multiple Sclerosis. Table 5.2 shows the product(s) that were identified as the most frequently purchased by muscle spasm patients (indicated by “X”), as well as the percentage of patients it represents from the 677 patients included in this analysis.

The most frequently purchased product for the majority of patients (70.2%) was a single product with a specific THC:CBD ratio and route of administration. The most common product purchased was a very high THC:CBD-inhaled product (32.3% of all patients) followed by a balanced-enteral and balanced-inhaled product (16.7% and 7.2%, respectively). For patients who purchased multiple products most frequently an equal number of times, the most common combination purchased was for a very high THC:CBD-inhaled product and a balanced-enteral product, accounting for 4.3% of all patients.

Table 5.2. Product(s) most frequently purchased by each muscle spasm patient (out of 677 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 677 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
					X										32.3 (219)	95.2 mg / 0.4 mg
		X													16.7 (113)	37.8 mg / 31.4 mg
							X								7.2 (49)	34.1 mg / 16.9 mg
X															5.3 (36)	69.0 mg / 0.3 mg
		X			X										4.3 (29)	115.7 mg / 64.8 mg
					X	X									4.0 (27)	89.2 mg / 15.0 mg
			X												2.8 (19)	9.9 mg / 190.1 mg
										X					2.8 (19)	41.0 mg / 0.2 mg
		X					X								2.4 (16)	46.3 mg / 27.9 mg
X					X										1.9 (13)	72.9 mg / 0.4 mg
												X			1.9 (13)	19.7 mg / 14.2 mg
X		X													1.5 (10)	57.0 mg / 18.4 mg
X		X			X										1.0 (7)	167.3 mg / 24.2 mg
X		X					X								1.0 (7)	67.2 mg / 18.3 mg
		X								X					1.0 (7)	60.0 mg / 23.8 mg
X		X			X	X									0.9 (6)	219.9 mg / 77.3 mg
		X	X												0.7 (5)	16.8 mg / 102.8 mg
		X			X	X									0.7 (5)	1449.9 mg / 370.4 mg
						X									0.7 (5)	150.9 mg / 8.9 mg
					X					X					0.6 (4)	111.8 mg / 0.6 mg
X										X					0.4 (3)	54.9 mg / 0.2 mg
		X	X				X								0.4 (3)	50.7 mg / 121.2 mg
	X				X										0.3 (2)	170.3 mg / 4.5 mg
			X		X										0.3 (2)	56.3 mg / 90.6 mg
			X				X								0.3 (2)	30.3 mg / 80.0 mg
					X	X									0.3 (2)	184.2 mg / 7.9 mg
										X		X			0.3 (2)	39.7 mg / 15.1 mg
X		X	X												0.3 (2)	38.1 mg / 89.9 mg
X					X					X					0.3 (2)	193.1 mg / 1.0 mg
X		X			X					X					0.3 (2)	107.6 mg / 14.2 mg

Table 5.2 Continued. Product(s) most frequently purchased by each muscle spasm patient (out of 677 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 677 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
	X														0.1 (1)	166.7 mg / 15.7 mg
				X											0.1 (1)	1.0 mg / 182.6 mg
X							X								0.1 (1)	131.4 mg / 18.2 mg
		X		X											0.1 (1)	10.1 mg / 205.5 mg
		X				X									0.1 (1)	80.7 mg / 24.3 mg
		X										X			0.1 (1)	37.4 mg / 37.4 mg
		X											X		0.1 (1)	12.8 mg / 153.4 mg
			X							X					0.1 (1)	16.2 mg / 40.0 mg
			X									X			0.1 (1)	153.9 mg / 919.7 mg
			X										X		0.1 (1)	33.9 mg / 644.0 mg
					X								X		0.1 (1)	88.5 mg / 99.2 mg
							X					X			0.1 (1)	59.0 mg / 41.0 mg
							X						X		0.1 (1)	34.2 mg / 67.2 mg
												X	X		0.1 (1)	39.7 mg / 146.9 mg
X	X	X													0.1 (1)	65.8 mg / 8.0 mg
X	X			X											0.1 (1)	106.1 mg / 201.4 mg
X	X				X										0.1 (1)	111.3 mg / 6.1 mg
X			X		X										0.1 (1)	113.8 mg / 47.7 mg
X					X		X								0.1 (1)	118.8 mg / 36.9 mg
	X				X		X								0.1 (1)	146.1 mg / 18.2 mg
		X	X							X					0.1 (1)	42.3 mg / 113.4 mg
		X	X									X			0.1 (1)	107.4 mg / 108.7 mg
		X			X					X					0.1 (1)	138.5 mg / 43.4 mg
		X			X							X			0.1 (1)	86.4 mg / 44.6 mg
		X					X			X					0.1 (1)	76.5 mg / 32.6 mg
		X								X		X			0.1 (1)	81.1 mg / 51.2 mg
			X	X			X								0.1 (1)	34.7 mg / 302.1 mg
			X		X		X								0.1 (1)	91.7 mg / 742.3 mg
					X		X			X					0.1 (1)	314.3 mg / 25.7 mg
					X		X					X			0.1 (1)	232.5 mg / 127.7 mg

Table 5.2 Continued. Product(s) most frequently purchased by each muscle spasm patient (out of 677 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 677 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
					X		X						X		0.1 (1)	117.1 mg / 112.0 mg
					X					X			X		0.1 (1)	88.3 mg / 47.9 mg
X		X	X				X								0.1 (1)	44.7 mg / 117.0 mg
	X	X			X		X								0.1 (1)	121.6 mg / 31.4 mg
		X	X		X		X								0.1 (1)	70.4 mg / 111.2 mg
		X	X				X					X			0.1 (1)	53.1 mg / 129.1 mg
		X			X		X			X					0.1 (1)	138.2 mg / 21.4 mg
		X				X	X					X			0.1 (1)	258.3 mg / 98.3 mg
			X	X	X					X					0.1 (1)	692.0 mg / 248.8 mg
X		X	X	X			X								0.1 (1)	86.0 mg / 6117.0 mg
X		X			X		X			X					0.1 (1)	135.6 mg / 10.6 mg
		X	X				X			X		X			0.1 (1)	65.8 mg / 69.9 mg
X		X	X	X	X		X								0.1 (1)	139.1 mg / 304.6 mg
X		X			X	X	X			X					0.1 (1)	303.9 mg / 27.8 mg
		X	X		X	X						X	X		0.1 (1)	189.7 mg / 130.6 mg
		X	X		X		X			X		X			0.1 (1)	161.6 mg / 848.6 mg

Cancer Patients

Of the 1529 patients represented in this analysis, 26.6% (406) of them were certified for Cancer. Table 5.3 shows the product(s) that were identified as the most frequently purchased by cancer patients (indicated by “X”), as well as the percentage of patients it represents from the 406 patients included in this analysis.

The majority of patients (61.6%) most frequently purchased a single product with a specific THC:CBD ratio and route of administration. Most commonly purchased products were a very high THC:CBD-inhaled product (23.9% of all patients) followed by a balanced-enteral and very high THC:CBD-oral mucosal product (10.3% and 9.6%, respectively). For patients who purchased multiple products most frequently an equal number of times, the most common combination purchased was for a very high THC:CBD product – one for enteral administration and one for inhalation (accounted for 5.4% of all patients).

Table 5.3. Product(s) most frequently purchased by each cancer patient (out of 406 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 406 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
					X										23.9 (97)	81.4 mg / 0.4 mg
		X													10.3 (42)	46.4 mg / 28.4 mg
										X					9.6 (39)	37.3 mg / 0.2 mg
X															5.9 (24)	108.0 mg / 0.5 mg
X					X										5.4 (22)	62.9 mg / 0.4 mg
							X								3.7 (15)	69.2 mg / 22.6 mg
					X					X					3.2 (13)	87.0 mg / 0.4 mg
		X					X								3.0 (12)	37.7 mg / 21.9 mg
												X			2.7 (11)	58.5 mg / 54.2 mg
		X			X										2.7 (11)	70.6 mg / 17.3 mg
			X												2.5 (10)	9.6 mg / 239.3 mg
X										X					2.2 (9)	45.5 mg / 0.2 mg
		X								X					2.2 (9)	111.8 mg / 39.0 mg
					X		X								1.7 (7)	68.7 mg / 13.7 mg
X		X					X								1.7 (7)	82.8 mg / 22.8 mg
				X											1.5 (6)	3.8 mg / 666.5 mg
X		X													1.5 (6)	47.6 mg / 9.5 mg
X					X					X					1.2 (5)	90.3 mg / 0.5 mg
	X														1.0 (4)	28.6 mg / 5.4 mg
X		X			X		X								1.0 (4)	102.0 mg / 25.3 mg
		X										X			0.7 (3)	72.7 mg / 48.6 mg
										X		X			0.7 (3)	51.2 mg / 7.2 mg
X		X			X										0.7 (3)	64.4 mg / 11.3 mg
X		X								X					0.7 (3)	54.1 mg / 8.7 mg
	X	X			X										0.7 (3)	94.4 mg / 11.3 mg
		X	X				X								0.7 (3)	24.2 mg / 92.5 mg
		X			X		X								0.7 (3)	80.9 mg / 13.3 mg
						X									0.5 (2)	3812.7 mg / 224.3 mg
		X	X												0.5 (2)	20.1 mg / 200.4 mg
			X							X					0.5 (2)	43.0 mg / 97.6 mg
					X	X									0.5 (2)	227.9 mg / 10.4 mg
							X					X			0.5 (2)	48.8 mg / 14.5 mg

Table 5.3 Continued. Product(s) most frequently purchased by each cancer patient (out of 406 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 406 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
													X		0.2 (1)	3.4 mg / 64.8 mg
X			X												0.2 (1)	33.1 mg / 150.1 mg
X												X			0.2 (1)	18.7 mg / 8.8 mg
	X	X													0.2 (1)	181.3 mg / 35.6 mg
	X		X												0.2 (1)	282.1 mg / 525.9 mg
			X		X										0.2 (1)	47.6 mg / 150.2 mg
					X							X			0.2 (1)	97.9 mg / 31.4 mg
					X								X		0.2 (1)	60.8 mg / 117.1 mg
												X	X		0.2 (1)	32.7 mg / 135.4 mg
X	X			X											0.2 (1)	106.1 mg / 201.4 mg
X		X	X												0.2 (1)	13.0 mg / 49.5 mg
X					X		X								0.2 (1)	185.0 mg / 20.5 mg
X					X							X			0.2 (1)	94.5 mg / 24.7 mg
		X			X					X					0.2 (1)	125.6 mg / 50.4 mg
					X		X					X			0.2 (1)	232.5 mg / 127.7 mg
X		X			X	X									0.2 (1)	427.4 mg / 64.7 mg
			X	X	X					X					0.2 (1)	692.0 mg / 248.8 mg
X	X	X	X		X										0.2 (1)	278.3 mg / 302.9 mg
X		X	X		X					X					0.2 (1)	135.4 mg / 296.4 mg
		X	X	X	X		X								0.2 (1)	184.5 mg / 237.7 mg
		X			X		X			X		X			0.2 (1)	128.8 mg / 16.4 mg
		X			X		X					X	X		0.2 (1)	154.6 mg / 139.8 mg

Seizure Patients

Of the 1529 patients represented in this analysis, 19.8% (303) of them were certified for Seizures, including those Characteristic of Epilepsy. Table 5.4 shows the product(s) that were identified as the most frequently purchased by seizure patients (indicated by “X”), as well as the percentage of patients it represents from the 303 patients included in this analysis.

89.1% of all patients most frequently purchased a single product with a specific THC:CBD ratio and route of administration. Most commonly used products were a high CBD:THC-enteral product (59.7% of all patients) followed by a very high THC:CBD-inhaled product and high CBD:THC-oral mucosal product (7.9% and 5.0%, respectively).

Table 5.4. Product(s) most frequently purchased by each seizure patient (out of 303), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 303 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
			X												59.7 (181)	8.3 mg / 170.6 mg
					X										7.9 (24)	75.2 mg / 0.4 mg
													X		5.0 (15)	2.7 mg / 130.4 mg
		X													4.6 (14)	31.1 mg / 24.8 mg
				X											4.3 (13)	7.9 mg / 1394.4 mg
							X								3.6 (11)	36.3 mg / 14.7 mg
												X			2.0 (6)	96.7 mg / 43.3 mg
			X	X											1.7 (5)	10.9 mg / 539.0 mg
X															1.3 (4)	7.8 mg / 0.0 mg
			X				X								1.3 (4)	72.7 mg / 815.1 mg
X		X													0.7 (2)	46.5 mg / 16.6 mg
		X	X												0.7 (2)	22.1 mg / 64.1 mg
		X					X								0.7 (2)	56.7 mg / 46.0 mg
					X		X								0.7 (2)	151.4 mg / 27.6 mg
							X							X	0.7 (2)	32.7 mg / 89.4 mg
X	X	X	X		X										0.3 (1)	278.3 mg / 302.9 mg
X		X	X												0.3 (1)	63.2 mg / 130.4 mg
X		X			X										0.3 (1)	55.3 mg / 3.2 mg
X		X					X								0.3 (1)	36.1 mg / 9.7 mg
X					X		X								0.3 (1)	64.3 mg / 17.7 mg
		X		X											0.3 (1)	10.1 mg / 205.5 mg
		X												X	0.3 (1)	10.0 mg / 100.0 mg
			X	X										X	0.3 (1)	16.5 mg / 492.9 mg
			X		X										0.3 (1)	75.2 mg / 723.6 mg
			X											X	0.3 (1)	33.9 mg / 644.0 mg
				X			X								0.3 (1)	19.0 mg / 217.9 mg
					X	X									0.3 (1)	204.3 mg / 7.3 mg
					X									X	0.3 (1)	88.5 mg / 99.2 mg
						X									0.3 (1)	170.0 mg / 10.0 mg
										X					0.3 (1)	18.0 mg / 0.1 mg
												X	X		0.3 (1)	39.7 mg / 146.9 mg

Crohn's Disease Patients

Of the 1529 patients represented in this analysis, 6.7% (103) of them were certified for Crohn's Disease. Table 5.5 shows the product(s) that were identified as the most frequently purchased by Crohn's patients (indicated by "X"), as well as the percentage of patients it represents from the 103 patients included in this analysis.

71.8% of all patients most frequently purchased a single product with a specific THC:CBD ratio and route of administration. Most commonly used products were a very high THC:CBD-inhaled product (28.2% of all patients) followed by a balanced-enteral and balanced-inhaled product (16.5% and 8.7%, respectively). For patients who purchased multiple products most frequently an equal number of times, the most common combination identified was for a balanced-enteral product and a very high THC:CBD-inhaled product, accounting for 4.9% of all patients.

Table 5.5. Product(s) most frequently purchased by each Crohn’s Disease patient (out of 103 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 103 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
					X										28.2 (29)	70.0 mg / 0.4 mg
		X													16.5 (17)	31.9 mg / 31.5 mg
							X								8.7 (9)	28.5 mg / 12.5 mg
			X												5.8 (6)	15.6 mg / 297.4 mg
		X			X										4.9 (5)	68.9 mg / 16.9 mg
										X					3.9 (4)	35.8 mg / 0.2 mg
						X									2.9 (3)	153.8 mg / 9.0 mg
X					X										2.9 (3)	81.9 mg / 0.6 mg
X															1.9 (2)	15.3 mg / 0.0 mg
												X			1.9 (2)	21.3 mg / 14.5 mg
													X		1.9 (2)	4.4 mg / 83.7 mg
X		X													1.9 (2)	27.8 mg / 13.2 mg
		X					X								1.9 (2)	42.5 mg / 27.9 mg
					X		X								1.9 (2)	68.5 mg / 7.3 mg
		X								X					1.0 (1)	31.2 mg / 15.1 mg
			X		X										1.0 (1)	48.9 mg / 65.8 mg
					X					X					1.0 (1)	65.3 mg / 0.4 mg
X		X			X										1.0 (1)	64.6 mg / 3.3 mg
X										X		X			1.0 (1)	80.0 mg / 25.8 mg
	X				X		X								1.0 (1)	146.1 mg / 18.2 mg
		X	X				X								1.0 (1)	27.5 mg / 57.5 mg
		X			X		X								1.0 (1)	57.0 mg / 11.6 mg
		X					X					X			1.0 (1)	137.5 mg / 87.5 mg
					X		X					X			1.0 (1)	112.1 mg / 35.9 mg
	X	X	X		X										1.0 (1)	112.6 mg / 47.1 mg
		X	X		X		X								1.0 (1)	97.8 mg / 109.5 mg
		X				X	X					X			1.0 (1)	258.3 mg / 98.3 mg
X		X	X	X			X								1.0 (1)	86.0 mg / 6117.0 mg
X		X			X		X			X		X			1.0 (1)	299.4 mg / 152.0 mg

Terminal Illness Patients

Of the 1529 patients represented in this analysis, 5.4% (82) of them were certified for Terminal Illness. Table 5.6 shows the product(s) that were identified as the most frequently purchased by terminal illness patients (indicated by “X”), as well as the percentage of patients it represents from the 82 patients included in this analysis.

68.3% of all patients most frequently purchased a single product with a specific THC:CBD ratio and route of administration. Most commonly used products were a very high THC:CBD-inhaled product (26.8% of all patients) followed by a balanced-enteral and balanced-orumucosal product (both respectively accounting for 8.5% of all patients). For patients who purchased multiple products most frequently an equal number of times, the most common combination identified was for a very high THC:CBD product – one for enteral administration and the other for oromucosal absorption (accounted for 3.7% of all patients).

Table 5.6. Product(s) most frequently purchased by each terminal illness patient (out of 82 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 82 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
					X										26.8 (22)	62.7 mg / 0.4 mg
		X													8.5 (7)	18.9 mg / 18.9 mg
												X			8.5 (7)	24.5 mg / 20.0 mg
										X					7.3 (6)	36.5 mg / 0.1 mg
X															6.1 (5)	17.2 mg / 0.0 mg
			X												6.1 (5)	9.8 mg / 188.2 mg
X										X					3.7 (3)	46.1 mg / 0.1 mg
		X					X								3.7 (3)	47.5 mg / 28.2 mg
								X							2.4 (2)	3812.7 mg / 224.3 mg
X					X										2.4 (2)	57.5 mg / 0.4 mg
		X			X										2.4 (2)	43.0 mg / 2.9 mg
					X					X					2.4 (2)	123.3 mg / 0.5 mg
X		X					X								2.4 (2)	104.5 mg / 25.7 mg
				X											1.2 (1)	5.2 mg / 925.0 mg
							X								1.2 (1)	36.4 mg / 9.1 mg
X		X													1.2 (1)	10.0 mg / 5.0 mg
	X	X													1.2 (1)	37.5 mg / 8.1 mg
		X	X												1.2 (1)	30.6 mg / 293.4 mg
					X		X								1.2 (1)	23.9 mg / 8.8 mg
					X								X		1.2 (1)	60.8 mg / 117.1 mg
							X			X					1.2 (1)	108.5 mg / 11.1 mg
X		X			X										1.2 (1)	66.0 mg / 20.3 mg
X					X					X					1.2 (1)	79.6 mg / 0.4 mg
		X			X		X								1.2 (1)	98.0 mg / 17.9 mg
			X	X	X					X					1.2 (1)	692.0 mg / 248.8 mg
X		X	X		X					X					1.2 (1)	135.4 mg / 296.4 mg
		X			X		X			X		X			1.2 (1)	128.8 mg / 16.4 mg

HIV/AIDS Patients

Of the 1529 patients represented in this analysis, 3.2% (49) of them were certified for Human Immunodeficiency Virus and/or Acquired Immune Deficiency Syndrome (HIV/AIDS). Table 5.7 shows the product(s) that were identified as the most frequently purchased by HIV/AIDS patients (indicated by “X”), as well as the percentage of patients it represents from the 49 patients included in this analysis.

75.5% of all patients most frequently purchased a single product with a specific THC:CBD ratio and route of administration. Most commonly used products were a very high THC:CBD-inhaled product (51.0% of all patients) followed by a balanced-enteral product (12.2% of patients). For patients who purchased multiple products most frequently an equal number of times, the most common combination identified was for two inhaled products – one of a very high THC:CBD ratio and the other a balanced THC:CBD ratio (accounted for 10.2% of all patients).

Table 5.7. Product(s) most frequently purchased by each HIV/AIDS patient (out of 49 patients), along with average daily THC/CBD dose (mg).

Enteral			Inhalation			Oromucosal				
Very High THC to CBD	High THC to CBD	Balanced	Very High THC to CBD	High THC to CBD	Balanced	Very High THC to CBD	High THC to CBD	Balanced	% of Patients out of 49 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
			X						51.0 (25)	93.4 mg / 0.6 mg
		X							12.2 (6)	45.4 mg / 35.9 mg
			X		X				10.2 (5)	76.8 mg / 13.7 mg
X									6.1 (3)	13.4 mg / 0.1 mg
					X				6.1 (3)	30.0 mg / 18.7 mg
		X	X						4.1 (2)	61.3 mg / 16.1 mg
X		X							2.0 (1)	20.0 mg / 15.0 mg
X						X			2.0 (1)	38.4 mg / 0.1 mg
		X			X				2.0 (1)	70.0 mg / 40.0 mg
		X				X			2.0 (1)	53.3 mg / 20.1 mg
			X	X					2.0 (1)	135.0 mg / 5.3 mg

Tourette Syndrome Patients

Of the 1529 patients represented in this analysis, 1.9% (29) of them were certified for Tourette Syndrome. Table 5.8 shows the product(s) that were identified as the most frequently purchased by Tourette Syndrome patients (indicated by “X”), as well as the percentage of patients it represents from the 29 patients included in this analysis.

93.1% of all patients most frequently purchased a single product with a specific THC:CBD ratio and route of administration. Most commonly used products were a balanced-enteral product (20.7% of all patients) followed by a very high THC:CBD-inhaled product and a very high THC:CBD-oral mucosal product (respectively at 20.7% and 13.8% of all patients).

Table 5.8. Product(s) most frequently purchased by each Tourette Syndrome patient (out of 29 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 29 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
		X													20.7 (6)	37.4 mg / 20.3 mg
					X										20.7 (6)	78.4 mg / 0.3 mg
										X					13.8 (4)	52.0 mg / 0.2 mg
X															10.3 (3)	21.2 mg / 0.1 mg
							X								10.3 (3)	51.8 mg / 20.1 mg
			X												6.9 (2)	33.4 mg / 633.7 mg
X		X			X		X								3.4 (1)	85.0 mg / 30.3 mg
	X									X					3.4 (1)	178.6 mg / 10.0 mg
	X														3.4 (1)	5812.5 mg / 93.0 mg
				X											3.4 (1)	13.4 mg / 2378.6 mg
												X			3.4 (1)	24.2 mg / 24.2 mg

Glaucoma Patients

Of the 1529 patients represented in this analysis, 1.5% (23) of them were certified for Glaucoma. Table 5.9 shows the product(s) that were identified as the most frequently purchased by glaucoma patients (indicated by “X”), as well as the percentage of patients it represents from the 23 patients included in this analysis.

56.5% of all patients most frequently purchased a single product with a specific THC:CBD ratio and route of administration. Most commonly used products were a very high THC:CBD-inhaled product (21.7% of all patients) followed by a very high THC:CBD-enteral product and a balanced-enteral product (respectively at 17.4% and 13.0% of all patients).

Table 5.9. Product(s) most frequently purchased by each glaucoma patient (out of 23 patients), along with average daily THC/CBD dose (mg).

Enteral			Inhalation			Oromucosal			% of Patients out of 23 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	Balanced	High CBD to THC	Very High THC to CBD	Balanced	High CBD to THC	Very High THC to CBD	Balanced	High CBD to THC		
			X						21.7 (5)	60.1 mg / 0.4 mg
X									17.4 (4)	54.5 mg / 0.3 mg
	X								13.0 (3)	7.1 mg / 3.2 mg
X	X								8.7 (2)	111.8 mg / 21.9 mg
			X	X					8.7 (2)	99.2 mg / 22.6 mg
X	X	X							4.3 (1)	255.0 mg / 195.8 mg
X						X	X		4.3 (1)	71.1 mg / 31.3 mg
X						X			4.3 (1)	61.7 mg / 0.3 mg
	X	X				X			4.3 (1)	42.3 mg / 113.4 mg
	X			X					4.3 (1)	32.0 mg / 8.0 mg
			X	X		X			4.3 (1)	115.9 mg / 31.6 mg
				X					4.3 (1)	40.0 mg / 10.0 mg

ALS Patients

Of the 1529 patients represented in this analysis, 1.4% (21) of them were certified for Amyotrophic Lateral Sclerosis (ALS). Table 5.10 shows the product(s) that were identified as the most frequently purchased by ALS patients (indicated by “X”), as well as the percentage of patients it represents from the 21 patients included in this analysis.

57.1% of all patients most frequently purchased a single product with a specific THC:CBD ratio and route of administration. Most commonly used product was a very high THC:CBD-inhaled product (14.3% of all patients).

Table 5.10. Product(s) most frequently purchased by each ALS patient (out of 21 patients), along with average daily THC/CBD dose (mg).

Enteral				Inhalation				Oromucosal				% of Patients out of 21 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC		
				X								14.3 (3)	44.8 mg / 0.3 mg
		X						X				9.5 (2)	54.9 mg / 26.6 mg
		X										9.5 (2)	16.1 mg / 7.5 mg
						X						9.5 (2)	25.6 mg / 18.1 mg
								X				9.5 (2)	29.8 mg / 0.1 mg
X								X				4.8 (1)	40.0 mg / 0.1 mg
X												4.8 (1)	16.0 mg / 0.0 mg
	X	X		X	X	X						4.8 (1)	205.5 mg / 24.4 mg
	X											4.8 (1)	20.8 mg / 3.9 mg
		X						X		X		4.8 (1)	81.1 mg / 51.2 mg
			X					X				4.8 (1)	27.1 mg / 80.1 mg
				X						X		4.8 (1)	101.2 mg / 8.7 mg
						X					X	4.8 (1)	26.1 mg / 220.8 mg
										X	X	4.8 (1)	22.2 mg / 120.8 mg
										X		4.8 (1)	28.4 mg / 28.4 mg

Medical Cannabis Use Patterns: Conclusions

To establish medication use patterns in program participants, a total of 16,238 product transactions were analyzed from 1529 patients in the 1st program year cohort. When product transactions were examined by each product's intended route of administration and THC:CBD content, the following patterns emerged. Firstly, roughly 90% of all products were purchased for enteral administration (through mouth via capsules or oral solutions) and inhalation (vaporized oil). Secondly, approximately 50% of all product transactions were for products very high in THC relative to CBD followed by balanced THC:CBD products (~30%) and high CBD:THC products (~15%). Very high THC:CBD products were most commonly purchased for inhalation or oromucosal absorption, while balanced and high CBD:THC products were most commonly used for enteral administration.

For this report, the most frequently purchased product(s) were identified for each patient as one method for understanding routine purchasing patterns. 72.5% of all patients most frequently purchased one type of product, with the most frequently purchased single product being a very high THC:CBD-inhaled product followed by a high CBD:THC-enteral and balanced-enteral product. For specific differences in the most frequently purchased products among qualifying conditions, the reader is encouraged to refer back to those specific sections.

6. Benefits

Summary

Information on patient benefits comes from the Patient Self-Evaluation (PSE) completed by patients prior to each medical cannabis purchase and from patient and health care practitioner surveys. Results of analysis of PSE and survey data indicate perceptions of a high degree of benefit for most patients.

Patients responded to a survey question asking them how much benefit they believe they received from using medical cannabis on a scale from 1 (no benefit) to 7 (great deal of benefit). Across all patients 64% indicated a benefit rating of 6 or 7 and this degree of benefit was indicated by at least half of the patients with each medical condition (see Table 6.1). A small but important proportion of patients indicated little or no benefit: 9% gave a rating of 1, 2, or 3. When patients were asked what the most important benefit was for them, two-thirds indicated a reduction in symptoms directly related to their qualifying medical condition and most of the remainder indicated more general quality of life benefits.

An important part of this report is the verbatim comments written by patients, and the reader is encouraged to review these comments in *Appendix A: Patient-Reported Benefits from Surveys*. Examples of these comments include:

- “Almost all muscle spasm and pain associated with spasms are gone. I used to have constant nerve triggered pain that is minimal now. Results were almost immediate. I am sleeping way better now also.”
- “[NAME] has passed away. I am her daughter and was her care giver. She was open to trying medical cannabis and we got the liquid form. It was a saving grace. She was in a lot of pain and when prescribed medications did NOT work – we started this and it kept her calm and relaxed. I am very thankful that we were able to have this option available. It helped to make her last months more bearable and truly it would have been miserable without it.”
- “I am getting enough sleep for the first time since about 2011. My absence seizures have gone from 3-4 a day to almost 0. It also has lessened the severity of grand mal seizures. The recovery time after has gone from around 12 hours to around 4.”
- “At first it helped a lot but my seizures have returned.”
- “Spasms – only a little better.”

Table 6.1. Patient-perceived benefit (n=792).

	No Response	1	2 or 3	4 or 5	6 or 7
All Patients	4%	4%	5%	23%	64%
Muscle Spasms	2%	3%	3%	22%	69%
Cancer	5%	5%	6%	21%	64%
Seizures	5%	5%	9%	29%	51%
Crohn's Disease	0%	2%	5%	22%	71%
Terminal Illness	11%	3%	3%	13%	71%
HIV/AIDS	4%	0%	8%	8%	79%
Tourette Syndrome	6%	0%	0%	25%	69%
Glaucoma	23%	8%	0%	0%	69%
ALS	9%	9%	0%	18%	64%

Patient responses about degree of benefit experienced: 1=no benefit; 7=great deal of benefit.

Health care practitioners were somewhat more conservative in assessment of benefit to their patients. Across all the benefit ratings by health care practitioners, 38% indicated a rating of 6 or 7 and 23% indicated little or no benefit (rating of 1, 2, or 3). Similarity in benefit assessment between health care practitioners and patients appears to vary by medical condition, with highest discrepancy among seizure patients. Descriptive comments suggest at least part of the difference is driven by perspective of what constitutes benefit. The patients cite quality of life benefits more often than the health care practitioners, who appear to focus more on objective measures such as seizure counts.

The symptom scores provided in the Patient Self-Evaluation data have the advantage of completeness, since they are required prior to each medical cannabis purchase. In this report a reduction of $\geq 30\%$ was applied to most symptoms to indicate clinically meaningful symptom reduction. In the text of the report, we present results for the more conservative of the two methods used to calculate $\geq 30\%$ symptom reduction. However, *Appendix D: Symptom Results*

from the Patient Self-Evaluation shows results for both methods (details can be found in this chapter). Results show patterns similar to those in the survey benefits rating, but usually somewhat smaller in size. For example, among patients with muscle spasms, weekly muscle spasm frequency was reduced $\geq 30\%$ within the first four months of medical cannabis use in 48% of patients (see Table 6.2). Importantly, in the four months after first achieving this degree of spasm reduction, more than half the patients retained this degree of improvement. That is, of all patients with muscle spasms, 48% achieved $\geq 30\%$ reduction in spasm frequency and 28% both achieved that degree of improvement and retained it over the next four months. Full results for symptom improvement analyses and for persistence of improvements are in *Appendix D: Symptom Results from the Patient Self-Evaluation*. Results for selected symptoms are presented in Table 6.2. For most symptoms, between half and two-thirds of patients who achieve clinically meaningful improvement retained that degree of improvement over the next four months.

Examples of proportion of patients achieving and retaining $\geq 30\%$ symptom reduction include:

- Among seizure patients, 68% reported $\geq 30\%$ reduction in seizure frequency and 49% both achieved that level of reduction and retained it, on average, for at least four months
- Among patients with Tourette syndrome, 61% reported $\geq 30\%$ reduction in tic frequency and 46% both achieved that level of reduction and retained it, on average, for at least four months
- Among patients with Crohn's disease, 51% reported $\geq 30\%$ reduction in number of liquid stools per day and 29% both achieved that level of reduction and retained it, on average, for at least four months
- Among patients with severe, persistent muscle spasms, 48% reported $\geq 30\%$ reduction in spasm frequency and 28% both achieved that level of reduction and retained it, on average, for at least four months
- Among cancer patients with at least moderate levels of nausea when they started using medical cannabis, 38% reported $\geq 30\%$ reduction of nausea and 23% both achieved that level of reduction and retained it, on average, for at least four months
- Among cancer patients with at least moderate levels of pain when they started using medical cannabis, 29% reported $\geq 30\%$ reduction of pain and 12% both achieved that level of reduction and retained it, on average, for at least four months

Moderate to severe levels of non-disease-specific symptoms such as fatigue, anxiety, and sleep difficulties were common across all the medical conditions. And the reductions in these symptoms was often quite large. These findings support the understanding that some of the benefit perceived by patients is expressed as improved quality of life.

The type(s) of medical cannabis used at the time patients achieved clinically meaningful improvement was analyzed for each symptom assessed within each category of medical condition. Full results of those analyses are in *Appendix D: Symptom Results from the Patient Self-Evaluation* and summaries are presented in this chapter. In most cases, a few combinations

of product types were purchased more frequently than others when analyzing data by patient condition

Table 6.2 Symptom improvement for selected symptoms. Note: for spasticity, pain, appetite, nausea, and vomiting the analysis was conducted on patients with moderate to severe symptoms at baseline.

	% of Patients who Achieved Threshold Symptom Improvement (≥30% Improvement Unless Otherwise Noted)	% of All Patients that Both Achieved Threshold Symptom Improvement and Retained that Degree of Improvement for at Least 4 Months
MUSCLE SPASMS		
Weekly spasm frequency (n = 629)	48%	28%
Spasticity (n = 618)	36%	17%
Pain (n = 640)	34%	17%
CANCER		
Pain (n = 356)	29%	12%
Appetite (n = 321)	39%	22%
Nausea (n = 283)	38%	23%
Vomiting (n = 168)	48%	27%
SEIZURES		
Weekly seizure frequency (n = 262)	68%	49%
CROHN'S DISEASE		
# Liquid stools/day (n = 41)	51%	29%
Abdominal pain (details in text; n = 73)	53%	19%
General well-being (details in text; n = 15)	47%	13%
Measures Combined (details in text; n = 102)	51%	22%
Weight (≥ 3 pound gain; n = 102)	21%	12%
TERMINAL ILLNESS		
Pain (n = 72)	19%	10%
Appetite (n = 64)	38%	17%
Nausea (n = 56)	45%	29%
Vomiting (n = 35)	57%	29%
HIV/AIDS		
Pain (n = 45)	40%	20%
Appetite (n = 39)	49%	31%
Weight (≥ 3 pound gain; n = 48)	15%	6%
TOURETTE SYNDROME		
Weekly tic frequency (n = 28)	61%	46%
GLAUCOMA (see text)		
ALS		
Weekly spasm frequency (n = 18)	33%	22%
Spasticity (n = 15)	20%	20%
Pain (n = 17)	47%	12%

Benefits Reported on Surveys

In addition to collecting data on severity of symptoms related to each patient's qualifying condition or conditions before each medical cannabis purchase, the Office of Medical Cannabis sought to gain a qualitative understanding of patient-reported benefits and harms of program participation. Utilizing expertise within the Minnesota Department of Health, the Office of Medical Cannabis developed a Patient Experience survey, which captures information on benefits and harms of program participation. A parallel survey was developed for each patient's certifying health care practitioner, which captures similar information from the clinician's perspective. The surveys include scaled response and open-response questions; health care practitioners were also asked to provide any clinical observations they noted about the patient's experience with medical cannabis. Healthcare providers familiar with the program provided feedback as part of the development process.

Survey Methodology and Data Preparation

The surveys are provided through an online platform with a hard copy alternative. The Patient Experience survey is sent three months after the patient's first medical cannabis purchase, six months after the first purchase and every six months thereafter. Healthcare practitioner surveys are sent six months after the patient's first purchase and every six months thereafter. Surveys are accessible through the patient or healthcare practitioner's registry page and through introductory emails containing unique links. To maximize survey submission rates, the survey can be submitted with incomplete responses to any of the questions. Each of the surveys is available online to the recipient for 45 days. Patient recipients receive reminder emails after one week; after two weeks with no response, paper copies of surveys are mailed to the recipient. For patients without online access the full process is accomplished by mail.

Initially, patient and healthcare practitioners (HCPs) were sent one survey three months after the patient's first purchase, without recurrence. This schedule was revised to include recurring surveys roughly every six months to provide patients and their HCPs an opportunity to report ongoing progress or changes to the patient's condition; however the HCP survey sent three months after the first purchase was eliminated based on feedback that three months may not allow enough time for the provider to see their patient following initial certification. These changes were implemented in April 2016; as a result, HCP survey data collected three months after the first purchase is only available for the first six months of the program (this includes patients who enrolled and made a first purchase between July 1, 2015 and December 31, 2015). All survey data presented in this chapter are from the patient and health care practitioner surveys sent three months after the patient's first medical cannabis purchase.

Patients and their certifying HCPs were asked to report the "most important benefit" and "most important negative effect" related to medical cannabis treatment. Survey responses from patients and health care practitioners on perceived benefits and perceived negative effects

were reported in free-text format; each response was individually reviewed and classified into a category of benefit or negative effects. Reported benefits typically included either direct improvement of symptoms related to the patient’s qualifying condition or more general improvements in health or quality of life, referred to in this report as global health benefits. Additionally, many responses included more than one type of benefit; in these cases, the first reported benefit was presumed to be the most important benefit. In this report, we examine both overall perceptions of benefit, as well as type of reported benefit.

Patient Experience Survey Results

Patient Experience Survey Response Rate

Of 1491 patients who were approved and made their first medical cannabis purchase in the first year of the program (July 1, 2015- June 30, 2016), 792 patients (53%) submitted a survey three months after making the first purchase. As of December 31, 2016, 90 patients (5%) were known to be deceased since enrolling in the program. These patients were included in this report, as in some cases caregivers or relatives and HCPs completed surveys, reflecting on the patient’s experience for the period of time the patient did use medical cannabis.

Table 6.3. Patient survey response rates by age group.

	Total	Patient Responses
0-4	62	17 (53%)
5-17	129	76 (59%)
18-24	89	51 (57%)
25-35	234	132 (56%)
36-49	355	192 (54%)
50-64	462	258 (56%)
65+	160	66 (41%)
Total	1491	792 (53%)

Table 6.4. Patient total counts and patient response rates by qualifying medical condition.

	Total	Patient Responses
Muscle Spasms	653	373 (57%)
Cancer	386	157 (41%)
Seizures	287	182 (63%)
Crohn's Disease	99	55 (56%)
Terminal Illness	79	38 (48%)
HIV/AIDS	46	24 (52%)
Tourette Syndrome	28	16 (57%)
Glaucoma	21	13 (62%)
ALS	21	11 (52%)

Table 6.5. Patient survey response rates by race and ethnicity.

	Total	Patient Responses
American Indian	37	14 (38%)
Asian	24	8 (33%)
Black	86	35 (41%)
Hawaiian	3	0 (0%)
White	1249	712 (57%)
Other	24	9 (38%)
Hispanic	35	14 (40%)

Patient response rates varied across age group, qualifying condition and race and ethnicity (Tables 6.3-6.5). Elderly patients (ages 65 and over) had the lowest response rate (41%); patients certified for cancer and terminal illness also had low response rates relative to other certified condition groups (41% and 48%, respectively). In general, racial and ethnic minorities were under-represented in survey responses.

Patient Perceptions of Benefits from Medical Cannabis

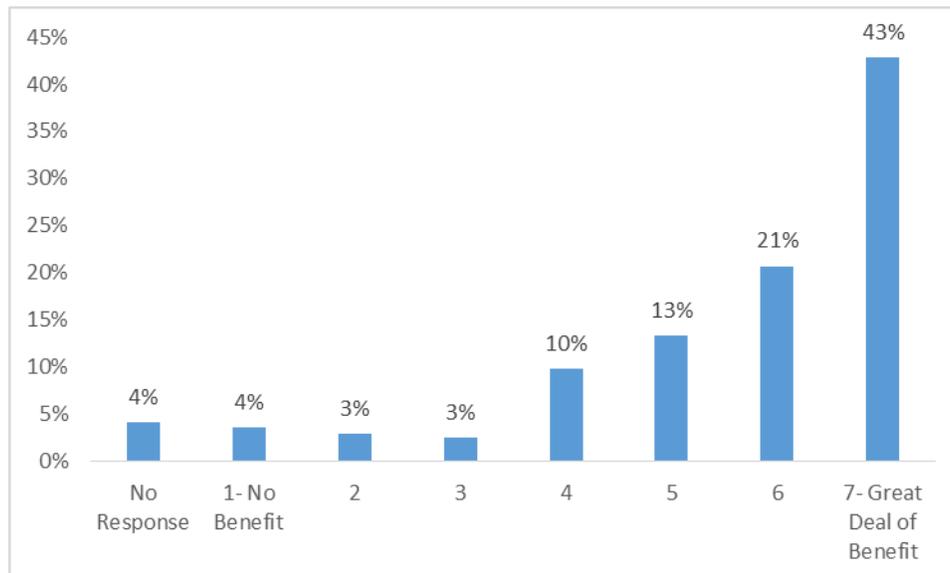
The Patient Experience and HCP surveys both ask respondents to report how much benefit they believe the patient received from using medical cannabis, on a scale from 1 (no benefit) to 7 (a great deal of benefit). Figures 6.1-6.10 show the distribution of benefit scores on this scale, as reported by patients, for all patients and by patients with each qualifying condition.

The percentages in Figures 6.1-6.10 are based on the total number of patient responses in each condition group and not the number of complete benefit scores for each group (33 patients submitted surveys without completing the benefit score question, but were included in the denominators).

ALL QUALIFYING CONDITIONS

Figure 6.1 below shows all patient responses about degree of benefit experienced. Among patient respondents, 43% report the highest degree of benefit from medical cannabis: “a great deal of benefit” or a score of 7 on a scale from 1-7.

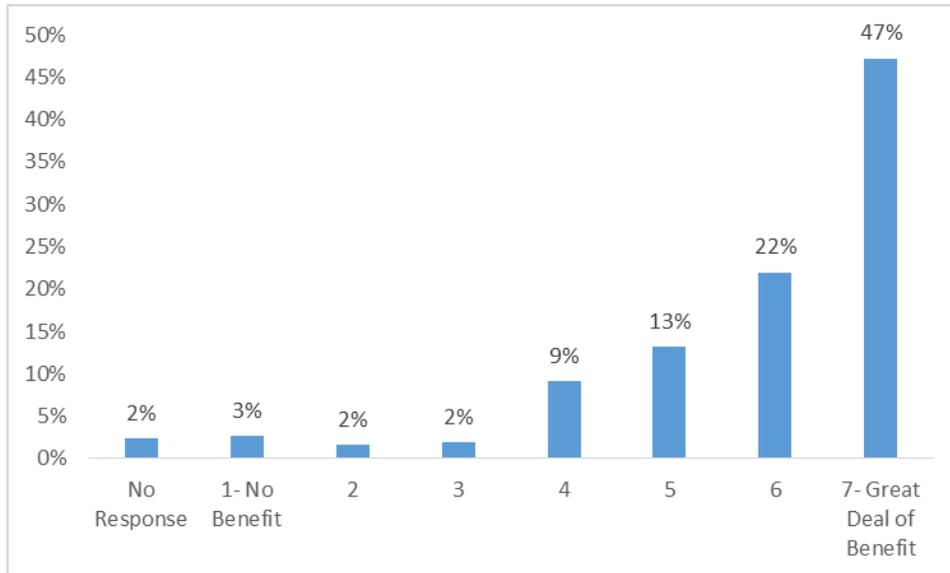
Figure 6.1. Patient-Perceived Benefit: All Conditions (N=792).



SEVERE AND PERSISTENT MUSCLE SPASMS

Figure 6.2 shows responses from patients certified for severe and persistent muscle spasms regarding degree of benefit experienced. Among respondents, 47% report a score of 7 on a scale from 1-7.

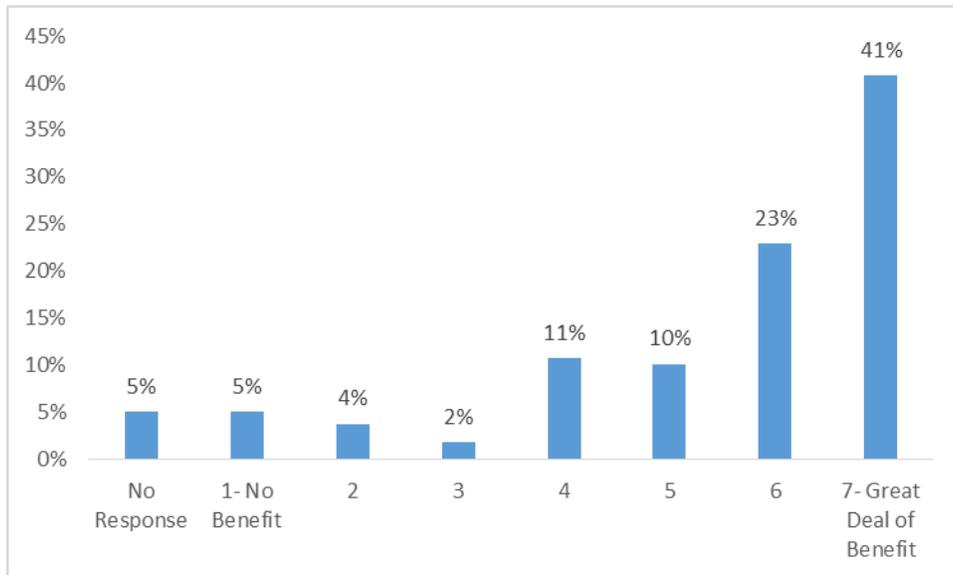
Figure 6.2. Patient-Perceived Benefit: Muscle Spasms (N=373)



CANCER

Figure 6.3 shows responses from patients certified for cancer regarding degree of benefit experienced. Among respondents, 41% report a score of 7 on a scale from 1-7.

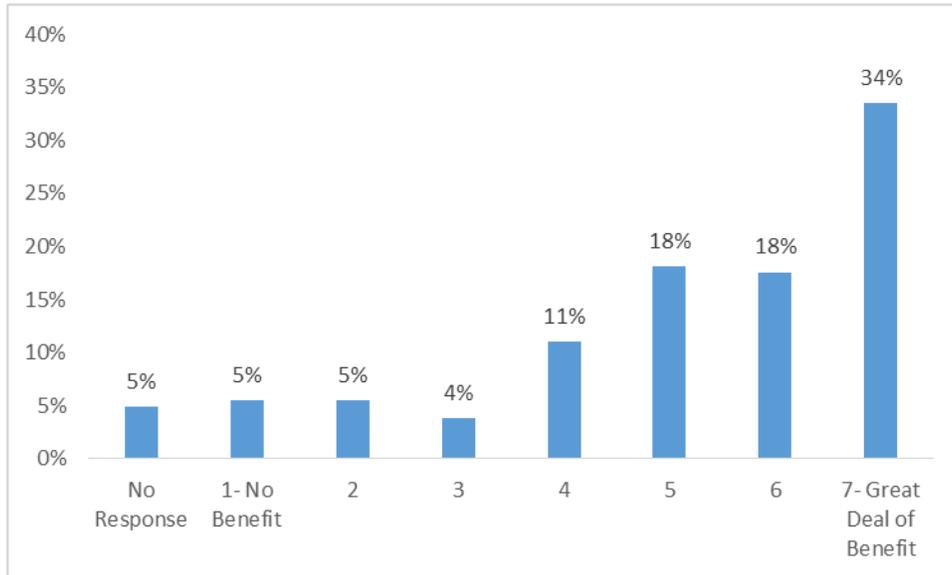
Figure 6.3. Patient-Perceived Benefit: Cancer (N=157)



SEIZURES

Figure 6.4 shows responses from patients certified for seizure disorders regarding degree of benefit experienced. Among respondents, 34% report a score of 7 on a scale from 1-7.

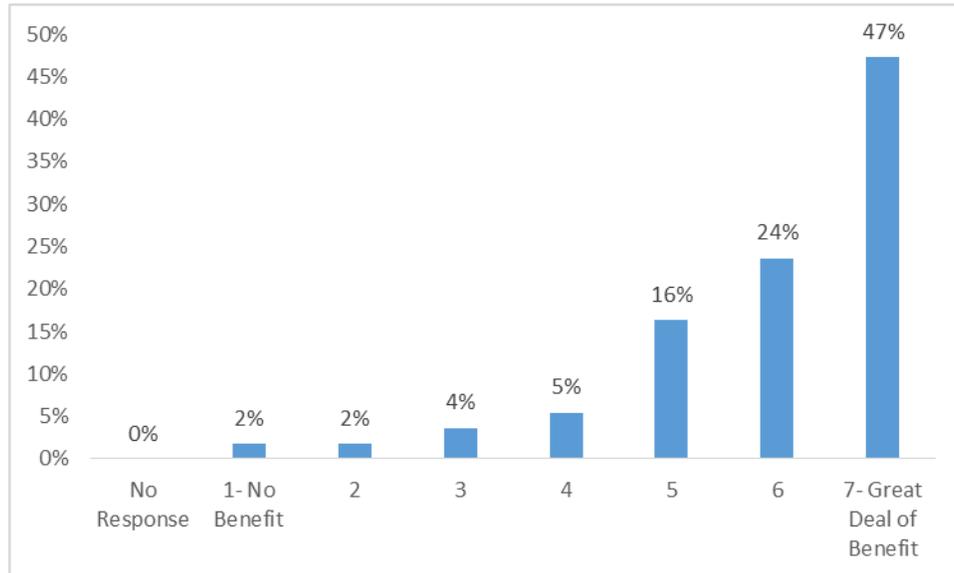
Figure 6.4. Patient-Perceived Benefit: Seizures (N=182)



CROHN'S DISEASE

Figure 6.5 shows responses from patients certified for Crohn's disease regarding degree of benefit experienced. Among respondents, 47% report a score of 7 on a scale from 1-7.

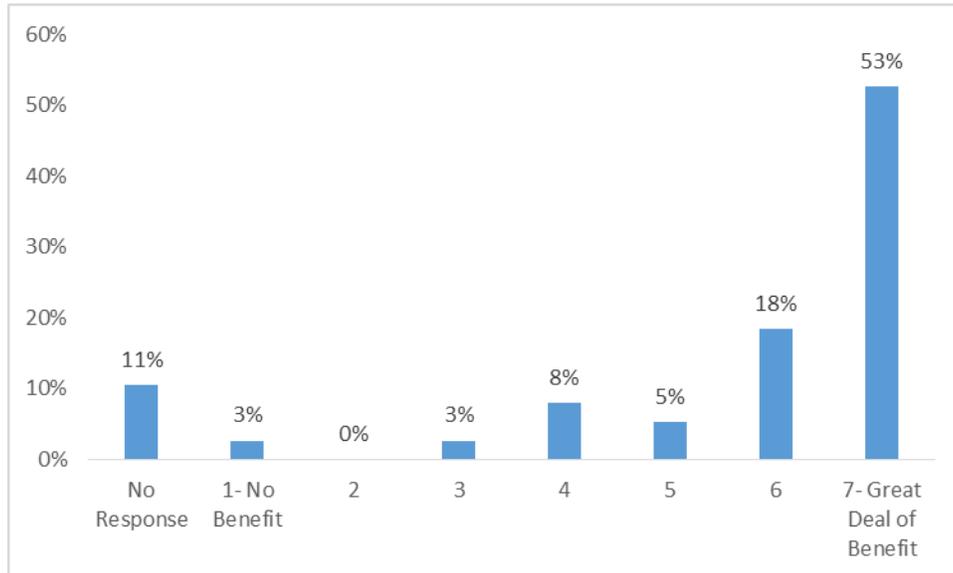
Figure 6.5. Patient-Perceived Benefit: Crohn's Disease (N=55)



TERMINAL ILLNESS

Figure 6.6 shows responses from patients certified for terminal illness regarding degree of benefit experienced. Among respondents, 53% report a score of 7 on a scale from 1-7.

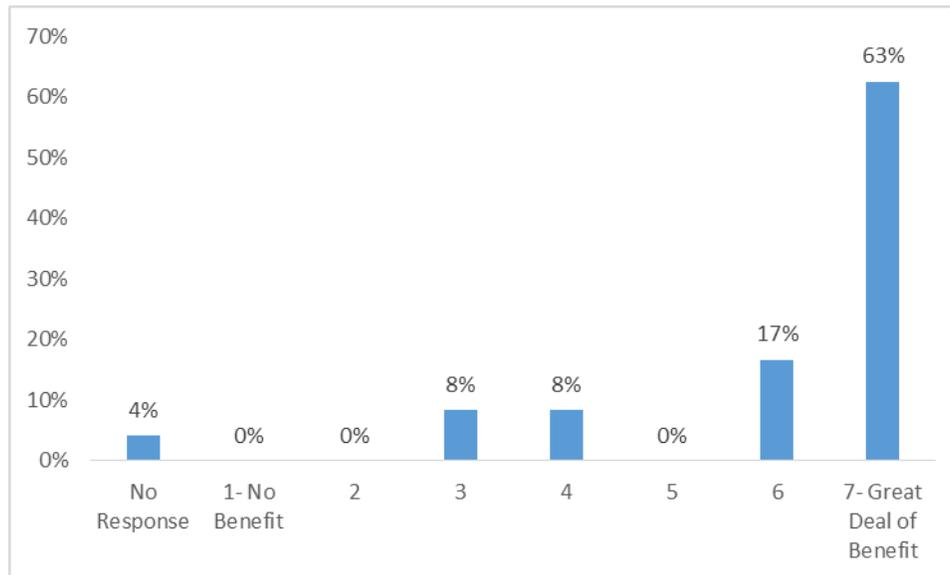
Figure 6.6. Patient-Perceived Benefit: Terminal Illness (N=38)



HIV/AIDS

Figure 6.7 shows responses from patients certified for HIV/AIDS regarding degree of benefit experienced. Among respondents, 63% report a score of 7 on a scale from 1-7.

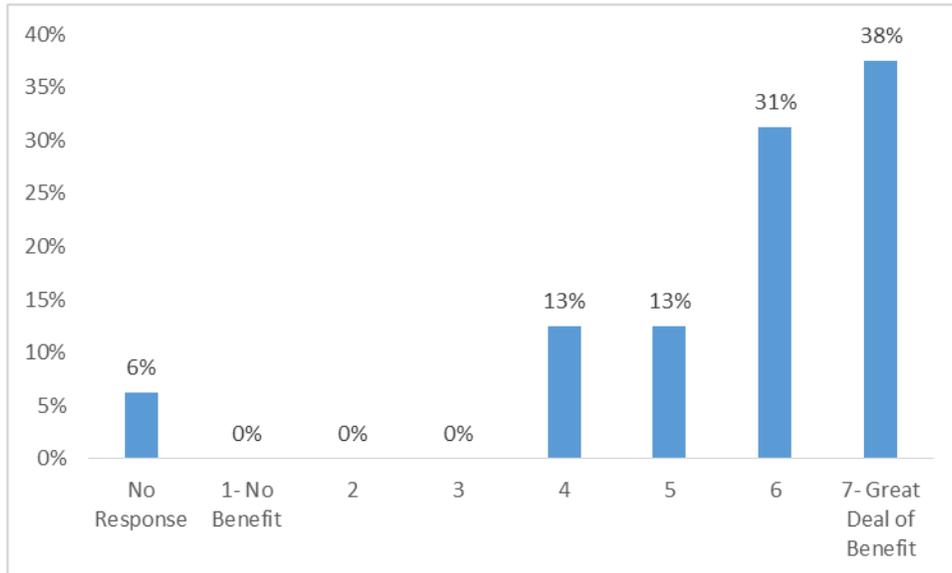
Figure 6.7. Patient-Perceived Benefit: HIV/AIDS (N=24)



TOURETTE SYNDROME

Figure 6.8 shows responses from patients certified for Tourette syndrome regarding degree of benefit experienced. Among respondents, 38% report a score of 7 on a scale from 1-7.

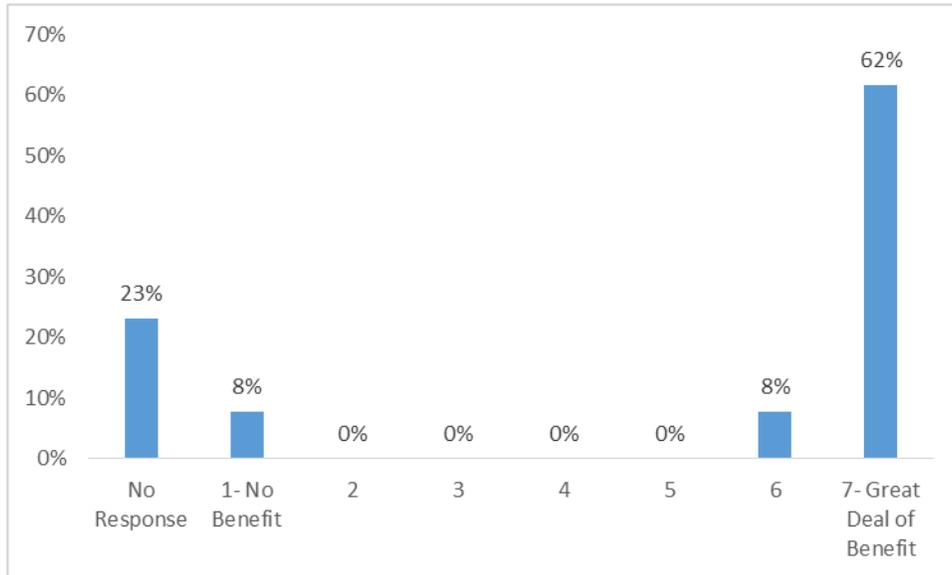
Figure 6.8. Patient-Perceived Benefit: Tourette Syndrome (N=16)



GLAUCOMA

Figure 6.9 shows responses from patients certified for glaucoma regarding degree of benefit experienced. Among respondents, 62% report a score of 7 on a scale from 1-7.

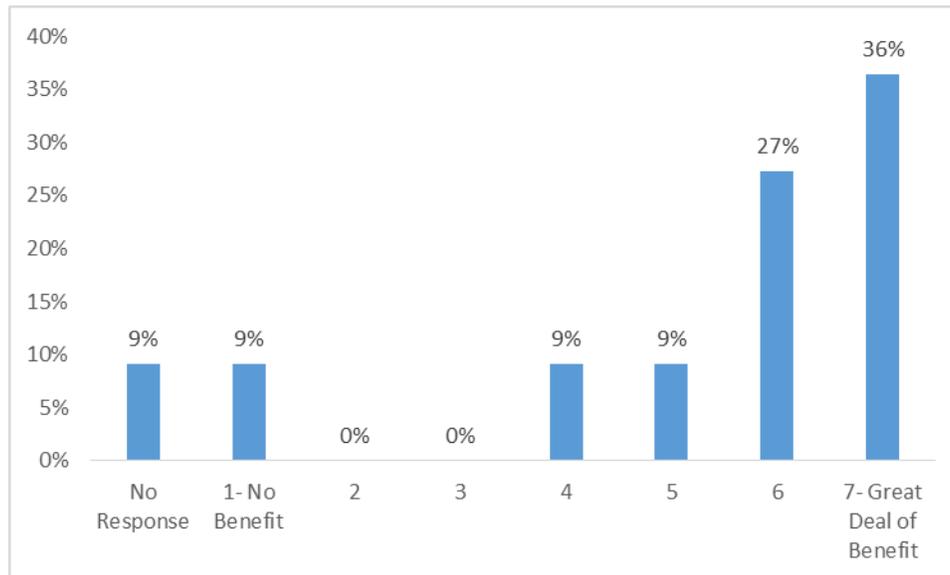
Figure 6.9. Patient-Perceived Benefit: Glaucoma (N=13)



ALS

Figure 6.10 shows responses from patients certified for ALS regarding degree of benefit experienced. Among respondents, 36% report a score of 7 on a scale from 1-7.

Figure 6.10. Patient-Perceived Benefit: ALS (N=11)



Patient Perceptions of Types of Benefits from Medical Cannabis Treatment

In both the Patient Experience and HCP surveys, patients and their certifying HCPs had an opportunity to describe the most significant benefit to the patient that was associated with medical cannabis treatment. Each response was reviewed and classified as symptom improvement (based on qualifying condition), or global health benefit, which included all health benefits not specifically related to the relief of symptoms directly associated with the patient's qualifying medical condition(s). Note that not all completed surveys had a response for this question; 86% of the Patient Experience surveys did and 66% of the HCP surveys did. Among the 681 completed Patient Experience survey responses that indicated a most significant benefit, 64% classified the benefit as symptom improvement and 25% classified it as a global health benefit; the remaining comments regarding benefit were improvement of symptoms other than those related to the qualifying condition or global health benefits. Tabulation of those responses is reported below, but the reader is also encouraged to read the verbatim responses in *Appendix A: Patient-Reported Benefits from Surveys*. Reading the words written by the patient gives a more nuanced understanding of the benefits and provides a reminder that each of the respondents is an individual person. The following is a selection of the comments, chosen to reflect the full range of benefits perceived:

- “Almost all muscle spasms and pain associated with spasms are gone. I used to have constant nerve triggered pain that is minimal now. Results were almost immediate. I am sleeping way better now also.”
- “A large reduction in symptoms, allowing me to participate in my daily life without a large number of limits my symptoms would place on me – stools decreased from over 8 a day to about 2 with much less blood and mucous in stools. Pain has reduced to a tolerable amount”
- “[NAME] has passed away. I am her daughter and was her care giver. She was open to trying medical cannabis and we got the liquid form. It was a saving grace. She was in a lot of pain and when prescribed medications did NOT work – we started this and it kept her calm and relaxed. I am very thankful that we were able to have this option available. It helped to make her last months more bearable and truly it would have been miserable without it.”
- “Has eased my muscle spasms and cramping. Has helped my visual issues. Has helped me to maintain healthy weight. Have been able to sleep much better and have cut other pain prescriptions way back. Seems to take pain away enough that I have been more active and am able to function on household tasks to a somewhat normal level. My brain seems to be working better as well ie. concentration/focusing and remembering.”
- “I am getting enough sleep for the first time since about 2011. My absence seizures have gone from 3-4 a day to almost 0. It also has lessened the severity of grand mal seizures. The recovery time after has gone from around 12 hours to around 4.”
- “Within 1 week of use, my tics disappeared and have stayed gone even with occasional use. This has never happened previously in my life, so it is very effective.”
- “At first it helped a lot but my seizures have returned.”
- “Spasms – only a little better.”

Symptom Improvement from Medical Cannabis Treatment

Table 6.6 summarizes the reported “most important benefits” which could be considered improvement of a symptom related to the patient’s qualifying condition from reports of patients, categorized by the benefit score reported by the patient. For patients with severe muscle spasms, reports of spasm reduction or pain reduction were considered symptom improvement. For patients with cancer (regardless of whether their condition was associated with severe/chronic pain, nausea or severe vomiting, cachexia or severe wasting, or a combination), pain reduction, nausea and/or vomiting reduction, and weight gain and/or appetite improvement were considered symptom improvement. For patients with seizures, reports of fewer seizures, less severe seizures, or both, were considered symptom improvement. For patients with Crohn’s disease, pain reduction, weight gain and/or appetite improvement, and reduction in related symptoms including stool frequency were considered symptom improvement. For patients with terminal illnesses (regardless of whether their condition was associated with severe/chronic pain, nausea or severe vomiting, cachexia or

severe wasting, or a combination), reduction in pain, nausea and/or vomiting and weight gain and/or appetite improvement were considered symptom improvement. For patients certified for HIV/AIDS, reduction in pain, nausea and/or vomiting, and weight gain and/or appetite improvement were considered symptom improvement. In patients with Tourette syndrome, reduced tics or specific mention of reduced Tourette symptoms were considered symptom improvement. In patients certified for glaucoma, reduction in intraocular pressure or reference to treatment of glaucoma “symptoms” was considered symptom improvement. Finally, for patients with ALS, reduction in pain or spasms were considered symptom improvement.

Among patients with severe and persistent muscle spasms, 26% reported pain reduction and another 25% reported spasm reduction as the most important benefit. Among seizure patients, 51% reported seizure reduction (either in frequency or severity). Among cancer patients, 26% reported pain reduction as the primary benefit; 25% reported weight gain, appetite improvement, or reduced nausea or vomiting. Among Crohn’s disease respondents, 25% reported reduced pain, 16% reported reduced severity or frequency of gastrointestinal symptoms and 4% reported weight gain or appetite improvement as the primary benefit. Among patients with terminal illness, 21% reported reduced nausea or vomiting, 18% reported pain reduction and 8% reported weight gain or appetite improvement as the most important benefit. Thirty-one percent of glaucoma patient respondents reported reduction of glaucoma-related symptoms. Among ALS patients, 27% reported pain reduction and 9% reported spasm reduction as the most important benefit. Among HIV/AIDS patients, 25% reported reduced pain, 17% reported reduced nausea and/or vomiting and 12% reported weight gain or appetite improvement as the most important benefit. Finally, among patients with Tourette syndrome, 63% reported a reduction in tics or other symptoms of Tourette syndrome.

Table 6.6. Distribution of Symptom Improvement by Condition: Patient Surveys

	1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
Muscle Spasms (n=373)								
<i>Spasm Reduction</i>	-	-	1 (0%)	11 (3%)	14 (4%)	24 (6%)	45 (12%)	95 (25%)
<i>Pain Reduction</i>	-	-	2 (1%)	6 (2%)	17 (5%)	24 (6%)	48 (13%)	97 (26%)
Cancer (n=157)								
<i>Pain Reduction</i>	-	-	-	3 (2%)	9 (6%)	12 (8%)	17 (11%)	41 (26%)

	1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
<i>Reduced Nausea/Vomiting</i>	-	-	-	1 (1%)	2 (1%)	2 (1%)	14 (9%)	19 (12%)
<i>Weight Gain/Appetite Improvement</i>	-	1 (1%)	-	2 (1%)	1 (1%)	6	10 (6%)	20 (13%)
Seizures (n=182)								
<i>Seizure Reduction</i>	-	3 (2%)	4 (2%)	9 (5%)	15 (8%)	22 (11%)	39 (21%)	92 (51%)
Crohn's Disease (n=55)								
<i>Pain Reduction</i>	-	-	-	-	3 (5%)	4 (5%)	7 (13%)	14 (25%)
<i>Reduced Crohn's Symptoms</i>	-	-	-	-	-	2 (4%)	7 (13%)	9 (16%)
<i>Weight Gain/Appetite Improvement</i>	-	-	-	-	1 (2%)	1 (2%)	-	2 (4%)
Terminal Illness (n=38)								
<i>Reduced Nausea/Vomiting</i>	-	-	-	1 (3%)	-	1 (3%)	6 (16%)	8 (21%)
<i>Pain Reduction</i>	-	-	-	1 (3%)	1 (3%)	-	5 (13%)	7 (18%)
<i>Weight Gain/Appetite Improvement</i>	-	-	-	-	-	-	3 (8%)	3 (8%)
HIV/AIDS (n=24)								
<i>Pain Reduction</i>	-	-	1 (4%)	1 (4%)	-	3 (13%)	3 (13%)	6 (25%)
<i>Reduced Nausea/Vomiting</i>	-	-	-	-	-	-	4 (17%)	4 (17%)

	1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
<i>Weight Gain/Appetite Improvement</i>	-	-	1 (4%)	-	-	-	2 (8%)	3 (12%)
Tourette Syndrome (n=16)								
<i>Reduced Tics/Tourette Symptoms</i>	-	-	-	-	1 (6%)	4 (25%)	5 (31%)	10 (63%)
Glaucoma (n=13)								
<i>Reduced Glaucoma Symptoms</i>	-	-	-	-	-	1 (8%)	3 (23%)	4 (31%)
ALS (n=11)								
<i>Spasm Reduction</i>	-	-	-	-	-	1 (9%)	-	1 (9%)
<i>Pain Reduction</i>	-	-	-	-	-	1 (9%)	2 (18%)	3 (27%)

Patient Perceptions of Global Health Benefits from Medical Cannabis

Many patients responded to the question regarding “most important benefit” by describing benefits not specifically related to the symptoms of their qualifying conditions. These responses were reviewed and classified into categories of “global health benefits”- broader benefits which impact the patient’s overall health. Global health benefits reported by patients included improvement in quality of life, improvement in sleep (whether or not explicitly tied to reduction in symptoms related to qualifying condition), improved mobility and/or ability to function or perform regular tasks, reduced anxiety or increased calmness, improved alertness and/or cognitive functioning, and reduced usage of other medications (often reported as reduction in dosage and/or side effects related to use of other medications). Clearly, global health benefits may be due to improvements in symptoms specifically related to the qualifying condition, so the dividing line between these categories is a bit blurry.

Table 6.7 shows the number of responses by type of global health benefit, along with the associated benefit score reported by the patient. Overall, 6% of patient respondents reported

improved sleep as the most important benefit from medical cannabis; 4% reported improved quality of life, 4% reported reduced usage of other medication, 3% reported reduced anxiety, and 2% reported improved alertness or cognitive function.

Table 6.7. Distribution of Global Health Benefits Condition: Patient Surveys

	1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
Muscle Spasms (n=373)								
<i>Weight Gain/ Appetite Improvement</i>	-	-	-	-	1 (0%)	3 (1%)	2 (1%)	6 (2%)
<i>Improved Alertness/ Cognitive Functioning</i>	-	-	-	-	-	-	1 (0%)	1 (0%)
<i>Improved Quality of Life</i>	-	-	2 (1%)	1 (0%)	1 (0%)	3 (1%)	10 (3%)	17 (5%)
<i>Improved Sleep</i>	-	1 (0%)	-	5 (1%)	7	4 (1%)	8 (2%)	25 (7%)
<i>Improved Mobility/Ability to Function</i>	-	1 (0%)	-	-	-	1 (0%)	10 (3%)	12 (3%)
<i>Decreased Anxiety</i>	-	1 (0%)	-	1 (0%)	-	5 (1%)	4 (1%)	11 (3%)
<i>Reduced Dosage and/or Side Effects of Other Medications</i>	-	-	-	-	-	2 (1%)	16 (4%)	18 (5%)
Cancer (n=157)								
<i>Reduced Anxiety</i>	-	1 (1%)	-	2 (1%)	-	1 (1%)	2 (1%)	6 (4%)
<i>Improved Sleep</i>	-	-	1 (1%)	2 (1%)	2 (1%)	1 (1%)	5 (3%)	11 (7%)
<i>Improved Quality of Life</i>	-	-	-	1 (1%)	-	2 (1%)	1 (1%)	4 (3%)
<i>Improved Alertness/Cognitive Functioning</i>	-	-	-	-	-	-	1 (1%)	1 (1%)

	1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
<i>Reduced Dosage and/or Side Effects of Other Medications</i>	-	-	-	-	-	2 (1%)	3 (2%)	5 (3%)
Seizures (n=182)								
<i>Decreased Anxiety</i>	-	1 (1%)	-	-	1 (1%)	-	-	2 (1%)
<i>Improved Sleep</i>	-	-	-	-	-	1 (1%)	1 (1%)	2 (1%)
<i>Reduced Dosage and/or Side effects of Other Medications</i>	-	-	-	-	1 (1%)	1 (1%)	3 (2%)	5 (3%)
<i>Improved Quality of Life</i>	-	-	-	-	2 (1%)	1 (1%)	4 (2%)	7 (4%)
<i>Improved Alertness/Cognitive Functioning</i>	-	2 (1%)	1 (1%)	3 (2%)	2 (1%)	5 (3%)	4 (2%)	17 (9%)
Crohn's Disease (n=55)								
<i>Improved Quality of Life</i>	-	-	-	1 (2%)	-	-	5 (9%)	6 (11%)
<i>Improved Sleep</i>	-	-	1 (2%)	2 (4%)	2 (4%)	1 (2%)	-	6 (11%)
<i>Decreased Anxiety</i>	-	-	-	-	1 (2%)	2 (4%)	-	3 (5%)
Terminal Illness (n=38)								
<i>Decreased Anxiety</i>	-	-	-	-	-	1 (3%)	-	1 (3%)
<i>Improved Alertness/ Cognitive Functioning</i>	-	-	-	-	-	-	1 (3%)	1 (3%)
<i>Improved Sleep</i>	-	-	1 (3%)	1 (3%)	-	-	2 (5%)	4 (11%)

	1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
<i>Improved Quality of Life</i>	-	-	-	-	-	2 (5%)	1 (3%)	3 (8%)
HIV/AIDS (n=24)								
<i>Improved Sleep</i>	-	-	-	-	-	-	1 (4%)	1 (4%)
<i>Decreased Anxiety</i>	-	-	-	-	-	-	2 (8%)	2 (8%)
Tourette Syndrome (n=16)								
<i>Improved Quality of Life</i>	-	-	-	-	-	-	1 (6%)	1 (6%)
<i>Decreased Anxiety</i>	-	-	-	1 (6%)	-	1 (6%)	-	2 (13%)
Glaucoma (n=13)								
<i>Improved Quality of Life</i>	-	-	-	-	-	-	1 (8%)	1 (8%)
ALS (n=11)								
<i>Reduced Anxiety</i>	-	-	-	1 (9%)	-	1 (9%)	1 (9%)	3 (27%)
<i>Improved Sleep</i>	-	-	-	-	1 (9%)	-	1 (9%)	2 (18%)

Health Care Practitioner Survey Results

HCP Survey Response Rate

As a result of changing the survey schedule during the first program year, the healthcare providers of 774 patients who were enrolled and made a first medical cannabis purchase in the first six months of the program (July 1 – December 31, 2015) received a survey three months after the patient’s first purchase; the remaining 717 could therefore not be included in the reporting below. The subset of Patient Experience survey responses that corresponds to this group of HCP responses is included below for comparison. Of 774 patients in this group, 437 patients (57%) submitted a survey three months after making the first purchase. Of the 262 health care practitioners (HCP) who certified these patients, 114 (43.5%) completed surveys for 251 (32%) patients.

Table 6.8. Healthcare Practitioner and Patient Experience survey response rates by age group.

	Total	HCP Responses	Patient Responses
0-4	15	7 (47%)	9 (60%)
5-17	90	36 (40%)	49 (54%)
18-24	48	18 (38%)	28 (58%)
25-35	110	32 (29%)	59 (54%)
36-49	194	66 (34%)	114 (59%)
50-64	225	65 (29%)	131 (58%)
65+	92	27 (29%)	47 (51%)
Total	774	251 (32%)	437 (58%)

Table 6.9. Patient total counts and HCP/patient response rates by qualifying medical condition.

	Total	HCP Responses	Patient Responses
Muscle Spasms	305	98 (32%)	182 (60%)
Cancer	192	51 (27%)	84 (44%)
Seizures	189	64 (34%)	120 (63%)
Crohn's Disease	58	25 (43%)	34 (59%)
Terminal Illness	43	12 (28%)	21 (49%)
HIV/AIDS	26	12 (46%)	15 (58%)
Tourette Syndrome	11	4 (36%)	6 (55%)
Glaucoma	11	3 (27%)	5 (45%)
ALS	15	5 (33%)	7 (47%)

Table 6.10. Patient total counts and HCP/patient response rates by race and ethnicity.

	Total	HCP Responses	Patient Responses
American Indian	16	6 (38%)	7 (44%)
Asian	17	8 (47%)	7 (41%)
Black	41	14 (35%)	15 (37%)
Hawaiian	1	0 (0%)	0 (0%)
White	665	218 (33%)	395 (59%)
Other	14	5 (36%)	6 (43%)
Hispanic	18	4 (22%)	6 (33%)

Response rates for the Patient Experience and HCP surveys varied widely across age group, qualifying condition and race and ethnicity (Tables 6.8-6.10). Patient response rate was lowest among the oldest age group (65+; 51%) and HCP response rate was generally lower for older age groups. Among HCP responses, certifiers of patients with HIV/AIDS and Crohn’s disease had the highest response rates (46% and 43%, respectively). Among patient responses, patients certified for severe and persistent muscle spasms, seizures and Crohn’s disease had the highest response rates (60%, 63%, and 59%, respectively). Finally, racial and ethnic minorities were generally under-represented among patient responses.

Healthcare Practitioner Perceptions of Benefit

The Patient Experience and HCP surveys both ask respondents to report how much benefit they believe the patient received from using medical cannabis, on a scale from 1 (no benefit) to 7 (a great deal of benefit). Figures 6.11-6.20 show the distribution of benefit scores on this scale, as reported by HCPs, for all patients and by patients with each qualifying condition.

A note on how proportions were calculated: the total number of HCP responses is reflected in Figures 6.11-6.20; this includes 45 HCP responses with either no response or a “0” option selected for the benefit scale, which indicates that the HCP did not have enough information about the patient to answer the question of benefit.)

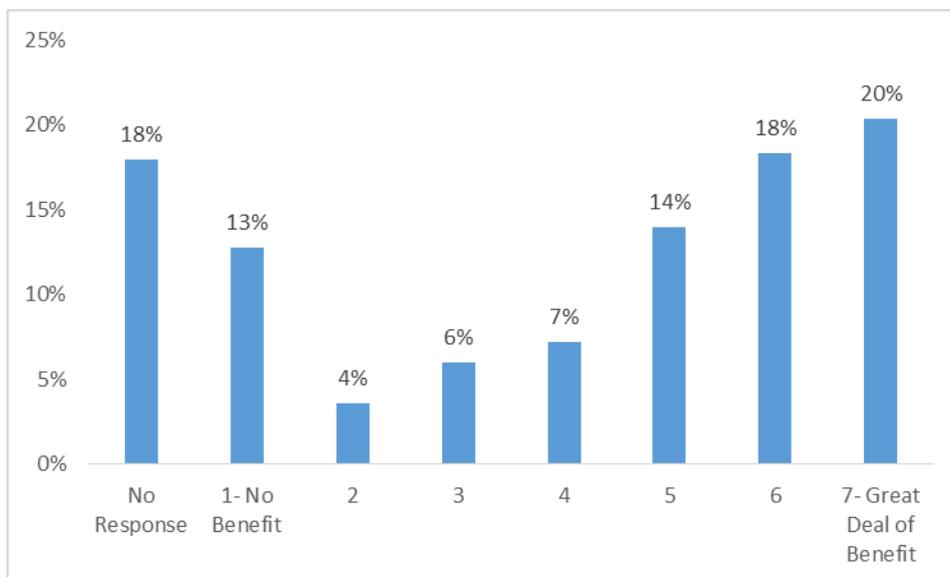
Note that results from patient surveys (Figures 6.1-6.10) and health care practitioner surveys (Figures 6.11-6.20) do not pertain to identical groups of patients. That is, some patients have

only a patient survey completed, some have only a HCP survey completed, some have neither completed, and some (n=126) have a completed survey from both the patient and their certifying HCP. For this reason, comparison of results from patient and HCP surveys must be approached with caution, except for the last group, where there is a completed survey from both the patient and the HCP. Further on in this section (Table 6.13 and Figures 6.21-6.28) comparisons for that last group are presented. In general, responses from HCPs report a lower degree of benefit than the patient responses.

ALL QUALIFYING CONDITIONS

Figure 6.11 shows all HCP responses about degree of benefit experienced. Benefit ratings were provided on 206 of the 251 submitted surveys. Among the 251 surveys, 32 (13%) reported no benefit and 51 (20%) reported the highest degree of benefit (score of 7); 150 (60%) reported a benefit score ≥ 4 on the seven-point scale.

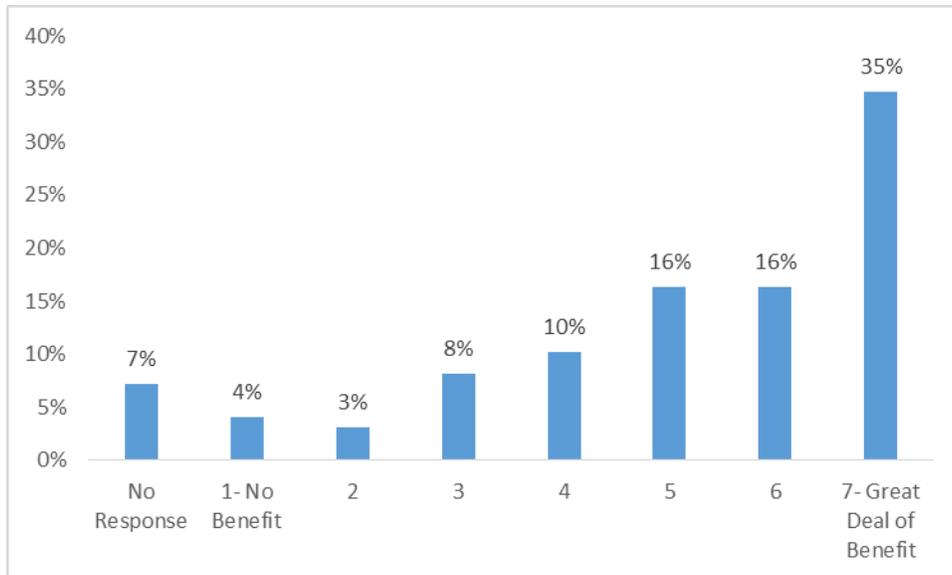
Figure 6.11. HCP-Perceived Benefit: All Conditions (N=251)



SEVERE AND PERSISTENT MUSCLE SPASMS

Figure 6.12 shows HCP benefit score responses for patients certified for severe and persistent muscle spasms. Benefit ratings were provided on 91 of the submitted surveys. Among the 91 responses, 4 reported no benefit and 34 reported the highest degree of benefit (score of 7); 76 (84%) reported a benefit score ≥ 4 on the seven-point scale.

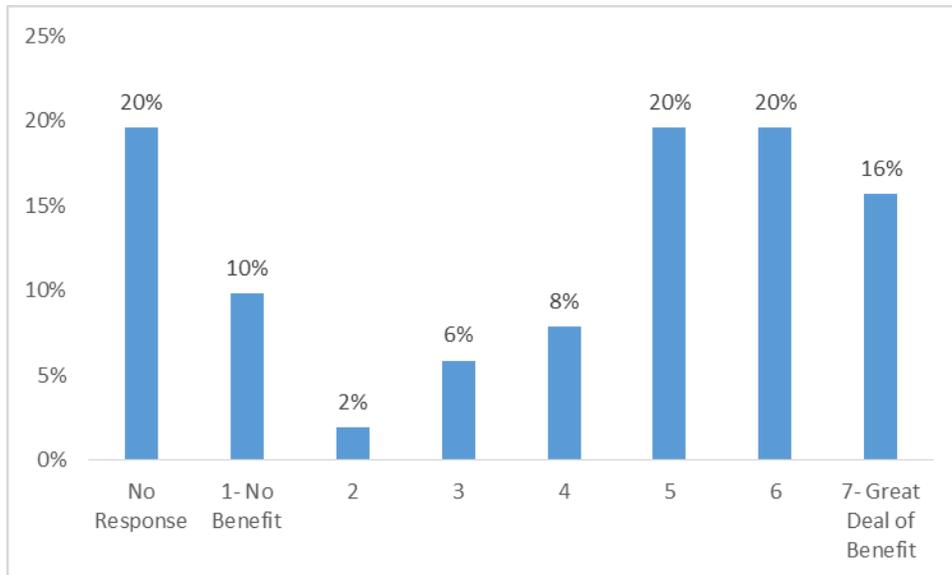
Figure 6.12. HCP-Perceived Benefit: Severe and Persistent Muscle Spasms (N=98)



CANCER

Figure 6.13 shows HCP benefit score responses for patients certified for cancer. Benefit ratings were provided on 41 of the submitted surveys. Among the 41 responses, 5 reported no benefit and 8 reported the highest degree of benefit (score of 7); 32 (78%) reported a benefit score ≥ 4 on the seven-point scale.

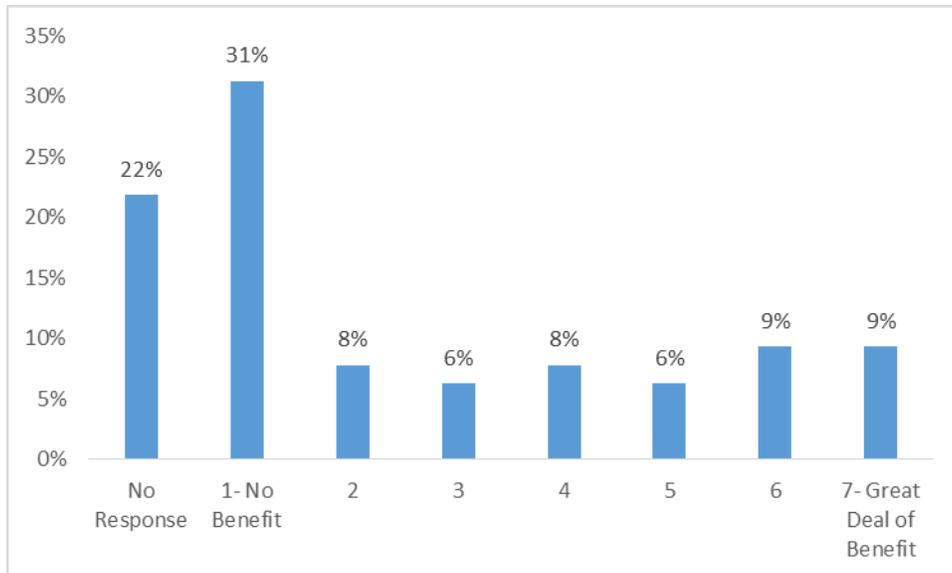
Figure 6.13. HCP-Perceived Benefit: Cancer (N=51)



SEIZURES

Figure 6.14 shows HCP benefit score responses for patients certified for seizures. Benefit ratings were provided on 50 of submitted surveys. Among the 50 responses, 20 reported no benefit and 6 reported the highest degree of benefit (score of 7); 21 (42%) reported a benefit score ≥ 4 on the seven-point scale.

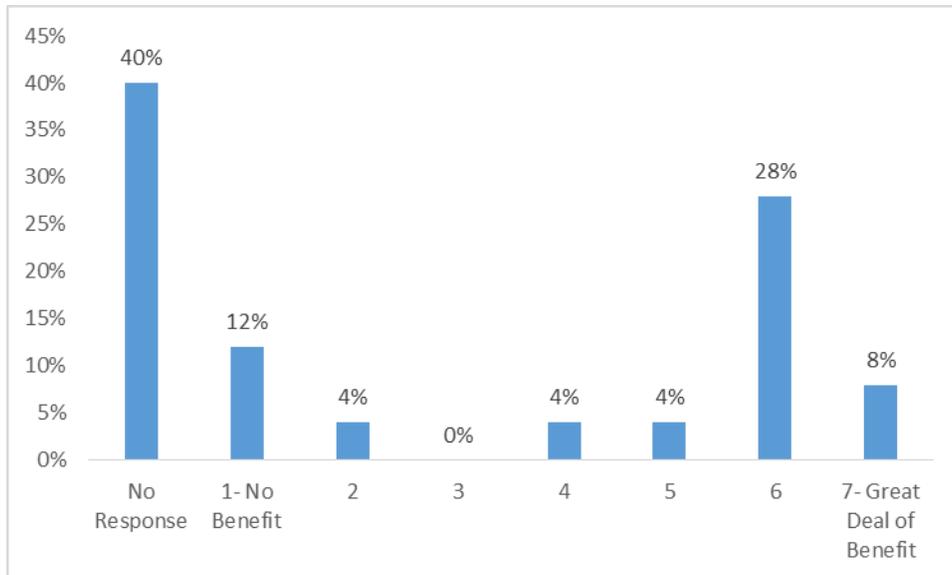
Figure 6.14. HCP-Perceived Benefit: Seizures (N=64)



CROHN'S DISEASE

Figure 6.15 shows HCP benefit score responses for patients certified for Crohn's disease. Benefit ratings were provided on 15 of the completed surveys. Among the 15 responses, 3 reported no benefit and 2 reported the highest degree of benefit (score of 7); 11 (73%) reported a benefit score ≥ 4 on the seven-point scale.

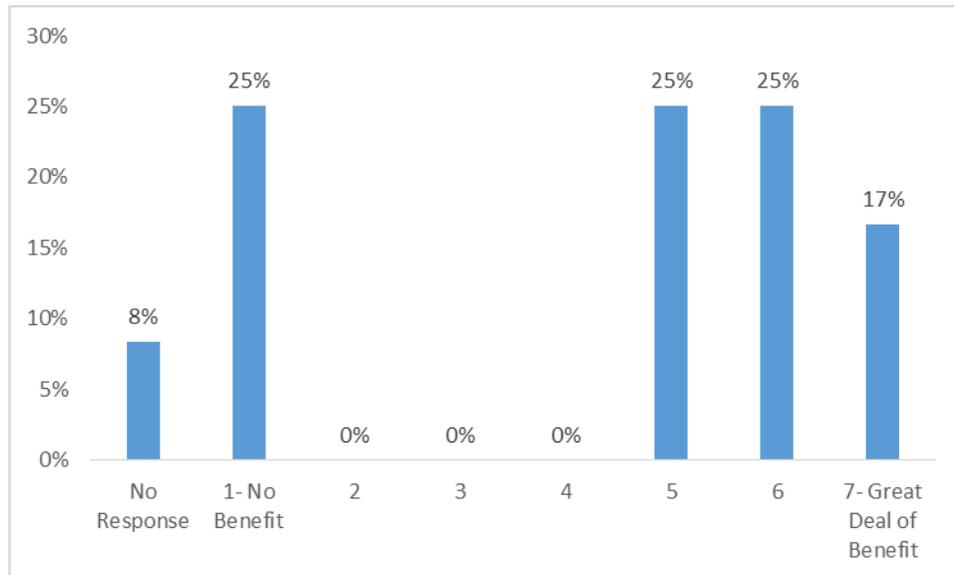
Figure 6.15. HCP-Perceived Benefit: Crohn's Disease (N=25)



TERMINAL ILLNESS

Figure 6.16 shows HCP benefit score responses for patients certified for terminal illness. Benefit ratings were provided on 11 of the completed surveys. Among the 11 responses, 3 reported no benefit and 2 reported the highest degree of benefit (score of 7); 8 (73%) reported a benefit score ≥ 4 on the seven-point scale.

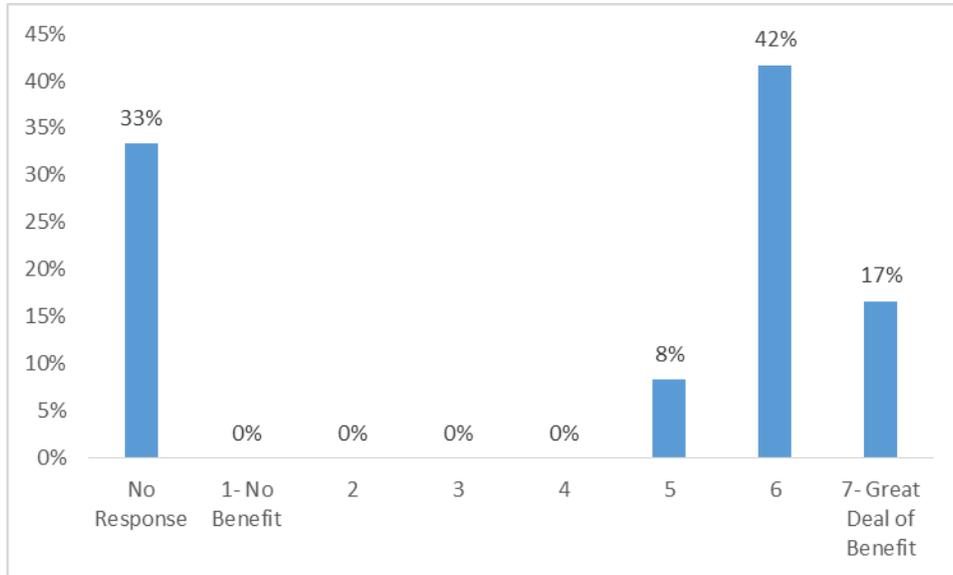
Figure 6.16. HCP-Perceived Benefit: Terminal Illness (N=12)



HIV/AIDS

Figure 6.17 shows HCP benefit score responses for patients certified for HIV/AIDS. Benefit ratings were provided on 8 of the 12 completed surveys. Among the 8 responses, none reported no benefit and two reported the highest degree of benefit (score of 7); all eight reported a benefit score ≥ 4 on the seven-point scale.

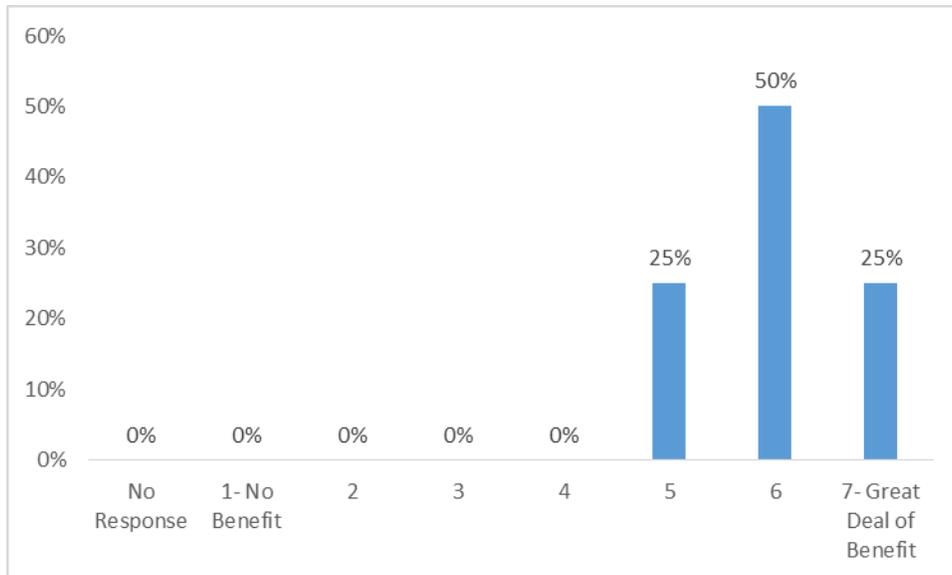
Figure 6.17. HCP-Perceived Benefit: HIV/AIDS (N=12)



TOURETTE SYNDROME

Figure 6.18 shows HCP benefit score responses for patients certified for Tourette syndrome. Benefit ratings were provided on all four of the completed surveys. Among the 4 responses, none reported no benefit and one reported the highest degree of benefit (score of 7); all four reported a benefit score ≥ 4 on the seven-point scale.

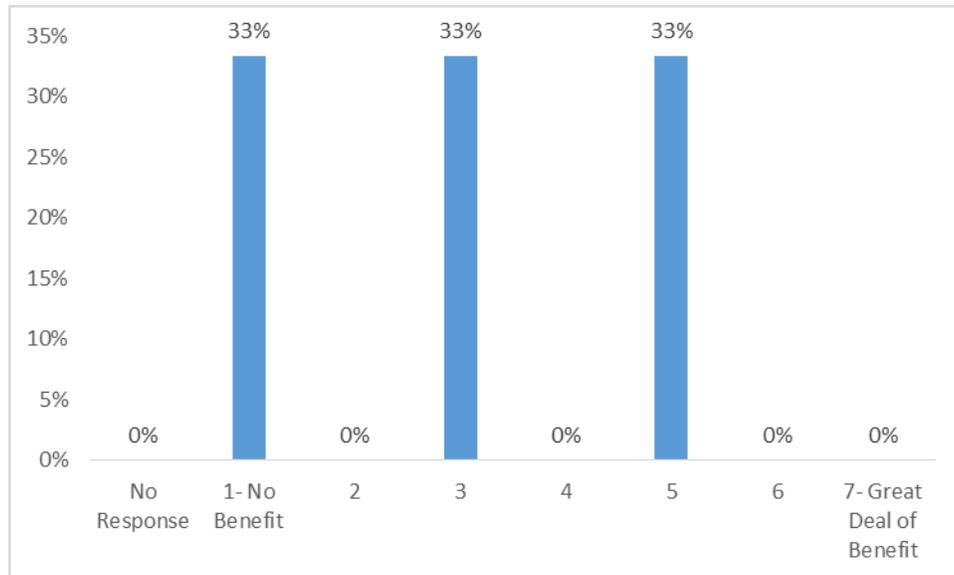
Figure 6.18. HCP-Perceived Benefit: Tourette Syndrome (N=4)



GLAUCOMA

Figure 6.19 shows HCP benefit score responses for patients certified for glaucoma. Benefit ratings were provided on all three of the completed surveys. Among the 3 responses, one reported no benefit and none reported the highest degree of benefit (score of 7); only one reported a benefit score ≥ 4 on the seven-point scale.

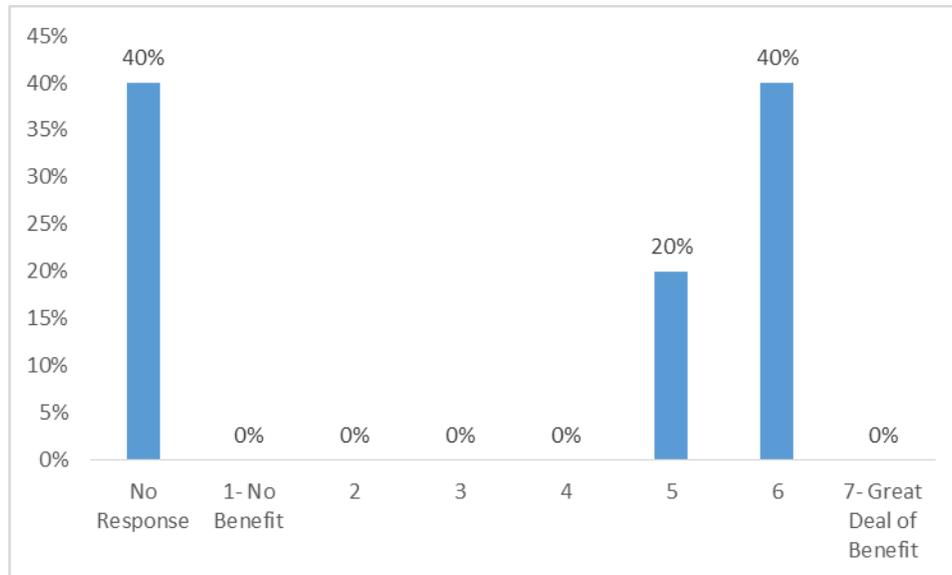
Figure 6.19. HCP-Perceived Benefit: Glaucoma (N=3)



ALS

Figure 6.20 shows HCP benefit score responses for patients certified for ALS. Benefit ratings were provided on 3 of the 5 completed surveys. Among the 3 responses, none reported no benefit and none reported the highest degree of benefit (score of 7); all three reported a benefit score ≥ 4 on the seven-point scale.

Figure 6.20. HCP-Perceived Benefit: ALS (N=5)



HCP Perceptions of Symptom Improvement from Medical Cannabis Treatment

Similar to the format in the Patient Experience survey, the HCP surveys asks certifying HCPs to describe the most significant benefit to the patient that is associated with medical cannabis treatment. Each response was reviewed and classified into broad categories of symptom improvement or global health benefits, as described in an earlier section. A full report of all benefit comments from HCPs can be found in *Appendix B: Healthcare Practitioner-Reported Benefits from Surveys*. Table 6 summarizes the reported “most important benefits” which could be considered improvement of a symptom related to the patient’s qualifying condition from reports of both patients and HCPs, again using a subset of patient responses from the same time window as HCP responses (surveys for patients making a first purchase between July 2015 and December 2015).

Table 6.11 Distribution of Symptom Improvement by Condition

Symptom Improvement by Score		1	2	3	4	5	6	7	Total
		(No Benefit)						(Great Deal of Benefit)	
Muscle Spasms									
Spasm Reduction	Patient (n=182)	-	-	-	6 (3%)	5 (3%)	14 (8%)	25 (14%)	50 (28%)
	HCP (n= 98)	-	-	1 (1%)	2 (2%)	6 (6%)	9 (9%)	9 (9%)	28 (29%)
Pain Reduction	Patient (n=182)	-	-	2 (1%)	3 (2%)	10 (6%)	10 (6%)	22 (12%)	47 (26%)
	HCP (n= 98)	-	1 (1%)	-	3 (3%)	4 (4%)	3 (3%)	11 (11%)	22 (22%)
Cancer									
Pain Reduction	Patient (n=84)	-	-	-	3 (4%)	7 (8%)	6 (7%)	7 (8%)	23 (27%)
	HCP (n= 51)	1 (2%)	-	2 (4%)	1 (2%)	2 (4%)	2 (4%)	2 (4%)	10 (20%)
Reduced Nausea/Vomiting	Patient (n=84)	-	-	-	1 (1%)	2 (2%)	1 (1%)	10 (12%)	14 (17%)

Symptom Improvement by Score		1	2	3	4	5	6	7	Total
		(No Benefit)						(Great Deal of Benefit)	
<i>Weight Gain/Appetite Improvement</i>	HCP (n= 51)	-	-	-	1 (2%)	5 (10%)	3 (6%)	4 (8%)	13 (26%)
	Patient (n=84)	-	-	-	-	1 (1%)	3 (4%)	7 (8%)	11 (13%)
	HCP (n= 51)	-	-	-	-	-	1 (2%)	-	1 (2%)
Seizures									
<i>Seizure Reduction</i>	Patient (n=120)	-	3 (3%)	1 (1%)	4 (3%)	11 (9%)	17 (14%)	31 (26%)	67 (56%)
	HCP (n= 64)	1 (2%)	2 (3%)	2 (3%)	2 (3%)	2 (3%)	5 (8%)	4 (6%)	18 (28%)
Crohn's Disease									
<i>Pain Reduction</i>	Patient (n=34)	-	-	-	-	2 (6%)	2 (6%)	4 (12%)	8 (24%)
	HCP (n= 25)	-	-	1 (4%)	-	-	3 (12%)	-	4 (16%)
<i>Reduced Gastrointestinal Symptoms</i>	Patient (n=34)	-	-	-	-	-	1 (3%)	4 (12%)	5 (15%)
	HCP (n= 25)	-	-	-	-	1 (4%)	-	1 (4%)	2 (8%)
<i>Weight Gain/Appetite Improvement</i>	Patient (n=34)	-	-	-	-	1 (3%)	1 (3%)	-	2 (9%)
	HCP (n= 25)	-	-	-	-	-	-	-	-
Terminal Illness									
<i>Reduced Nausea/Vomiting</i>	Patient (n=21)	-	-	-	1 (5%)	-	1 (5%)	4 (19%)	6 (29%)

Symptom Improvement by Score		1	2	3	4	5	6	7	Total
		(No Benefit)						(Great Deal of Benefit)	
<i>Pain Reduction</i>	HCP (n= 12)	-	-	-	-	1 (8%)	1 (8%)	1 (8%)	3 (25%)
	Patient (n=21)	-	-	-	1 (5%)	-	-	4 (19%)	5 (24%)
	HCP (n= 12)	-	-	-	-	1 (8%)	-	1 (8%)	2 (17%)
	Patient (n=21)	-	-	-	-	-	-	2 (10%)	2 (10%)
<i>Weight Gain/Appetite Improvement</i>	HCP (n= 12)	-	-	-	-	1 (8%)	1 (8%)	-	2 (17%)
	HIV/AIDS								
<i>Pain Reduction</i>	Patient (n=15)	-	-	1 (7%)	-	-	1 (7%)	3 (20%)	5 (33%)
	HCP (n= 12)	-	-	-	-	1 (8%)	1 (8%)	-	2 (17%)
<i>Reduced Nausea/Vomiting</i>	Patient (n=15)	-	-	-	-	-	-	3 (20%)	3 (20%)
	HCP (n= 12)	-	-	-	-	-	2 (17%)	-	2 (17%)
<i>Weight Gain/Appetite Improvement</i>	Patient (n=15)	-	-	-	-	-	-	2 (13%)	2 (13%)
	HCP (n= 12)	-	-	-	-	-	-	-	-
Tourette Syndrome									
<i>Reduced Tics/Tourette Symptoms</i>	Patient (n=6)	-	-	-	-	1 (17%)	-	3 (50%)	4 (67%)
	HCP (n= 5)	-	-	-	-	-	2 (40%)	1 (20%)	3 (60%)

Symptom Improvement by Score		1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
Glaucoma									
<i>Reduced Glaucoma Symptoms</i>	Patient (n=5)	-	-	-	-	-	-	2 (40%)	2 (40%)
	HCP (n= 3)	-	-	1 (33%)	-	-	-	-	1 (33%)
ALS									
<i>Spasm Reduction</i>	Patient (n=7)	-	-	-	-	-	1 (14%)	-	1 (14%)
	HCP (n= 5)	-	-	-	-	1 (20%)	1 (20%)	-	2 (40%)
<i>Pain Reduction</i>	Patient (n=7)	-	-	-	-	-	1 (14%)	2 (29%)	3 (43%)
	HCP (n= 5)	-	-	-	-	-	1 (20%)	-	1 (20%)

Patients represented in Patient Experience survey responses and in HCP responses were different; thus a direct comparison cannot be made between the proportions of patients and HCPs reporting any given benefit. However, it is worth noting that relatively high levels of symptom improvement benefit (most scores are above 4) are seen in both patient and HCP survey results. Among patient respondents certified for muscle spasms, 22% report spasm reduction at a high degree of benefit (scores of 6 or 7) and 18% of HCP responses for patients with muscle spasms report spasm reduction at a high degree of benefit. Among responses of patients certified for seizures, 40% reported reduction in seizure number or severity at a high degree of benefit; among HCP responses for patients with seizures, 14% reported seizure reduction (severity or frequency) at a high degree of benefit. Among patient responders certified for cancer, 15% reported pain reduction at a high degree of benefit; 13% reported reduced nausea or vomiting at a high degree of benefit and 12% reported weight gain or appetite improvement at a high degree of benefit. Among HCP responses for patients certified for cancer, 8% reported pain reduction at a high degree of benefit, 14% reported reduced nausea or vomiting and 2% reported weight gain or appetite improvement at a high degree of benefit.

HCP Perceptions of Global Health Benefits from Medical Cannabis Treatment

Table 6.12 summarizes responses to the Patient Experience and HCP surveys about the most significant benefit to the patient that were not classified as improvement of symptoms related to the qualifying medical condition.

As with Table 6.11, the proportion of patients reporting a type of global health benefit cannot be directly compared to the proportion of HCPs reporting a type of global health benefit to the patient because each group of responders is different. However, in general a higher proportion of the patient responses report a global health benefit as the primary benefit from medical cannabis than HCP responses and generally global health benefits are reported at a relatively high degree of perceived benefit (scores of 4 or greater).

Overall, 1% of HCP respondents and 6% of patient respondents reported improved sleep as the most important benefit from medical cannabis; 3% of HCP respondents and 4% of patients reported improved quality of life; 2% of HCP reports and 3% of patient reports cited reduced usage of other medications or related side effects as the most important benefit.

A full report of all benefit comments from HCPs can be found in *Appendix B: Healthcare Practitioner-Reported Benefits from Surveys*.

Table 6.12 Distribution of Global Health Benefits by Condition

Global Health Benefits by Score		1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
Muscle Spasms									
<i>Improved Quality of Life</i>	Patient (n=182)	-	-	-	-	-	2 (1%)	3 (2%)	5 (3%)
	HCP (n= 98)	-	-	-	1 (1%)	1 (1%)	1 (1%)	1 (1%)	4 (4%)
<i>Improved Sleep</i>	Patient (n=182)	-	-	-	2 (1%)	3 (2%)	3 (2%)	6 (3%)	14 (8%)
	HCP (n= 98)	-	-	-	1 (1%)	-	-	1 (1%)	2 (2%)
<i>Improved Mobility/Ability to Function</i>	Patient (n=182)	-	1 (1%)	-	-	-	-	6 (3%)	7 (4%)
	HCP (n= 98)	-	-	-	-	-	-	-	-
<i>Decreased Anxiety</i>	Patient (n=182)	-	-	-	-	-	1 (1%)	2 (1%)	3 (2%)
	HCP (n= 98)	-	-	1 (1%)	-	-	-	-	1 (1%)

Global Health Benefits by Score		1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
<i>Reduced Usage of Other Medications</i>	Patient (n=182)	-	-	-	-	-	-	6 (3%)	6 (3%)
	HCP (n= 98)	-	-	-	-	-	1 (1%)	3 (3%)	4 (4%)
Cancer									
<i>Reduced Anxiety</i>	Patient (n=84)	-	-	-	1 (1%)	-	-	1 (1%)	2 (2%)
	HCP (n= 51)	-	-	-	-	-	-	-	-
<i>Improved Sleep</i>	Patient (n=84)	-	-	1 (1%)	-	1 (1%)	-	5 (6%)	7 (8%)
	HCP (n= 51)	-	-	-	-	-	-	-	-
<i>Improved Quality of Life</i>	Patient (n=84)	-	-	-	-	-	1 (1%)	1 (1%)	2 (2%)
	HCP (n= 51)	-	-	-	-	1 (2%)	-	-	1 (2%)
<i>Improved Alertness/Cognitive Functioning</i>	Patient (n=84)	-	-	-	-	-	-	1 (1%)	1 (1%)
	HCP (n= 51)	-	-	-	-	-	-	-	-
<i>Reduced Usage of Other Medications</i>	Patient (n=84)	-	-	-	-	-	1 (1%)	3 (4%)	4 (5%)
	HCP (n= 51)	-	-	-	-	-	-	-	-
Seizures									
<i>Improved Sleep</i>	Patient (n=120)	-	-	-	-	-	1 (1%)	-	1 (1%)
	HCP (n= 64)	-	-	-	-	-	-	-	-
<i>Reduced Usage of Other Medications</i>	Patient (n=120)	-	-	-	-	-	-	1 (1%)	1 (1%)
	HCP (n= 64)	-	-	-	-	-	-	-	-
<i>Improved Quality of Life</i>	Patient (n=120)	-	-	-	-	2 (2%)	1 (1%)	1 (1%)	4 (3%)
	HCP (n= 64)	-	-	-	1 (2%)	-	-	-	1 (2%)

Global Health Benefits by Score		1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
<i>Improved Alertness/Cognitive Functioning</i>	Patient (n=120)	-	2 (2%)	1 (1%)	3	2 (2%)	4 (8%)	1 (1%)	13 (11%)
	HCP (n= 64)	-	-	-	-	-	-	-	-
Crohn's Disease									
<i>Improved Quality of Life</i>	Patient (n=34)	-	-	-	-	-	-	4 (12%)	4 (12%)
	HCP (n= 25)	-	-	-	-	-	-	-	-
<i>Improved Sleep</i>	Patient (n=34)	-	-	1 (3%)	1 (3%)	1 (3%)	1 (3%)	-	4 (12%)
	HCP (n= 25)	-	-	-	1 (4%)	-	-	-	1 (4%)
<i>Decreased Anxiety</i>	Patient (n=34)	-	-	-	-	-	1 (3%)	-	1 (3%)
	HCP (n= 25)	-	-	-	-	-	1 (4%)	-	1 (4%)
Terminal Illness									
<i>Improved Alertness/ Cognitive Functioning</i>	Patient (n=21)								
	HCP (n= 12)	-	-	-	-	-	-	1 (8%)	1 (8%)
<i>Improved Sleep</i>	Patient (n=21)	-	-	1 (5%)	-	-	-	2 (10%)	3 (14%)
	HCP (n= 12)	-	-	-	-	-	-	-	-
<i>Reduced Usage of Other Medications</i>	Patient (n=21)	-	-	-	-	-	-	-	-
	HCP (n= 12)	-	-	-	-	-	1 (8%)	-	1 (8%)
<i>Improved Quality of Life</i>	Patient (n=21)	-	-	-	-	-	1 (5%)	1 (5%)	2 (10%)
	HCP (n= 12)	-	-	-	-	-	-	-	-
HIV/AIDS									
<i>Improved Quality of Life</i>	Patient (n=15)	-	-	-	-	-	-	-	-

Global Health Benefits by Score		1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
<i>Improved Sleep</i>	HCP (n= 12)	-	-	-	-	-	-	1 (8%)	1 (8%)
	Patient (n=15)	-	-	-	-	-	-	1 (7%)	1 (7%)
	HCP (n= 12)	-	-	-	-	-	-	-	-
	Patient (n=15)	-	-	-	-	-	-	-	-
<i>Decreased Anxiety</i>	HCP (n= 12)	-	-	-	-	-	1 (8%)	-	1 (8%)
Tourette Syndrome									
<i>Improved Quality of Life</i>	Patient (n=6)	-	-	-	-	-	-	1 (2%)	1 (2%)
	HCP (n= 5)	-	-	-	-	-	-	-	-
Glaucoma									
<i>Improved Sleep</i>	Patient (n=5)	-	-	-	-	-	-	-	-
	HCP (n= 3)	-	-	-	-	1 (33%)	-	-	1 (3%)
ALS									
<i>Reduced Anxiety</i>	Patient (n=7)	-	-	-	-	-	1 (14%)	1 (14%)	2 (29%)
	HCP (n= 5)	-	-	-	-	-	-	-	-

Additional Clinical Observations

Healthcare practitioners were asked to provide any additional clinical observations or insights on the impact of medical cannabis treatment on the patient’s condition, and were specifically prompted to report any observations on drug interactions. A third of the 114 observations describe a decrease in the patients’ other medications- mainly opioids and benzodiazepines. The survey healthcare practitioners will complete for patients certified for intractable pain will ask specifically about this issue. There were a few comments about drug interactions with anti-epileptic drugs, including in some cases the anticipated ability to decrease dose of Clobazam. A full report of these observations can be found in *Appendix C: Healthcare Practitioner-Reported Clinical Observations from Surveys*.

Patient Versus HCP Perceptions of Benefit from Medical Cannabis

Among survey respondents, there were 126 patients who submitted a survey for whom their certifying health care practitioner also completed a survey. Comparison of benefit scores reported by the patient to benefit scores reported by the healthcare practitioner are shown in Table 6.13, grouping scores of 1 or 2 in a category representing no or little benefit; scores of 3, 4, or 5 were grouped into a category representing mild or moderate benefit and scores of 6 or 7 were placed in a category representing strong benefit. Among these 126 patients and their HCPs, 81 (64%) of patient-HCP pairs were in general agreement regarding degree of benefits experienced: 46% reported strong benefit from medical cannabis; 15% reported mild or moderate benefit and 3% reported no or little benefit (Table 6.13). When interpreting the meaning of these comparisons, it must be kept in mind that the 126 patients for whom both Patient Experience and HCP survey results are available are not necessarily representative of all patients who enrolled in the program during its first year of operation.

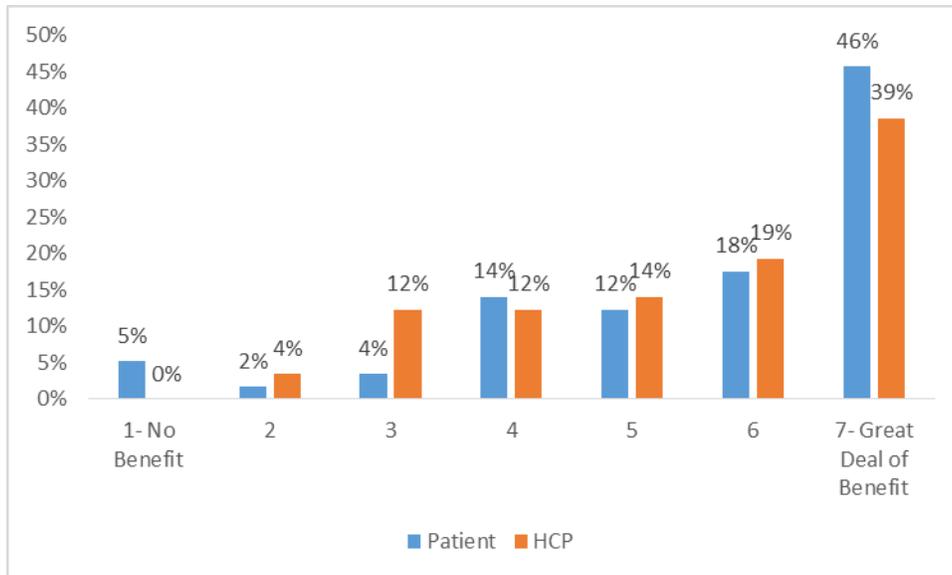
Table 6.13. Distribution of patient-reported benefits and HCP-reported benefits for patients with both patient and HCP surveys completed (n=126).

	HCP-Perceived Benefit		
Patient-Perceived Benefit	No/Little Benefit (1-2)	Mild/Moderate Benefit (3-5)	Strong Benefit (6-7)
No/Little Benefit (1-2)	4 (3%)	1 (1%)	2 (2%)
Mild/Moderate Benefit (3-5)	7 (6%)	19 (15%)	10 (8%)
Strong Benefit (6-7)	2 (2%)	23 (18%)	58 (46%)

Severe and Persistent Muscle Spasms

Figure 6.21 shows benefit scores reported by patients and their certifying HCPs for muscle spasms patients for whom both scores were available (n=57). Comparison of proportions of patients and HCPs reporting each benefit score shows fairly good agreement: 46% of patients and 39% of HCPs report scores of 6 or 7; 5% of patients and 0% HCPs report no benefit.

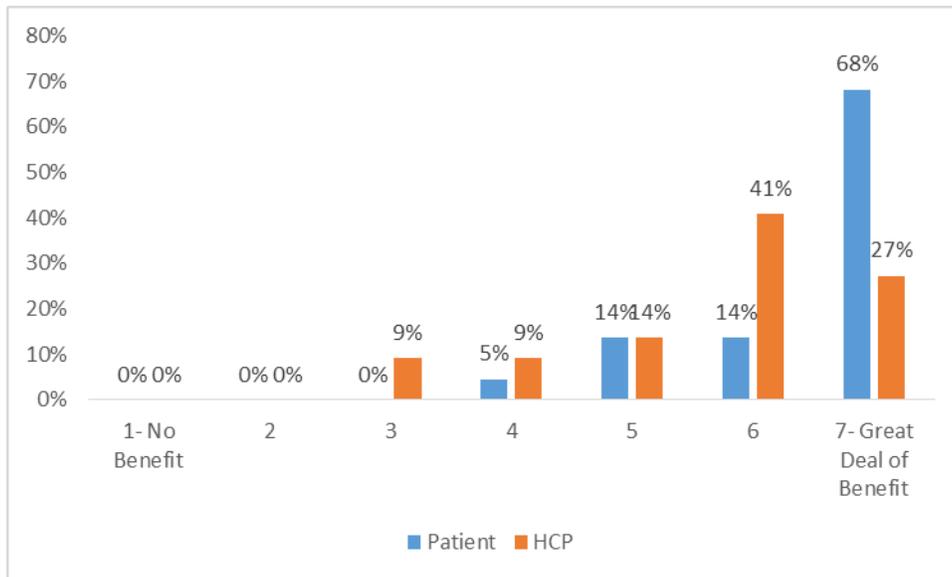
Figure 6.21. Muscle Spasms (N=57): Perceived Benefit



Cancer

Figure 6.22 shows benefit scores reported by patients and their certifying HCPs for cancer patients for whom both scores were available (n=22). Comparison of proportions of patients and HCPs reporting each benefit score shows differences in effect size but general agreement that patients experienced some benefit. Among this group, 68% of patients and 27% of HCPs report scores of 6 or 7; 0% patients and 0% HCPs report scores of 1 or 2.

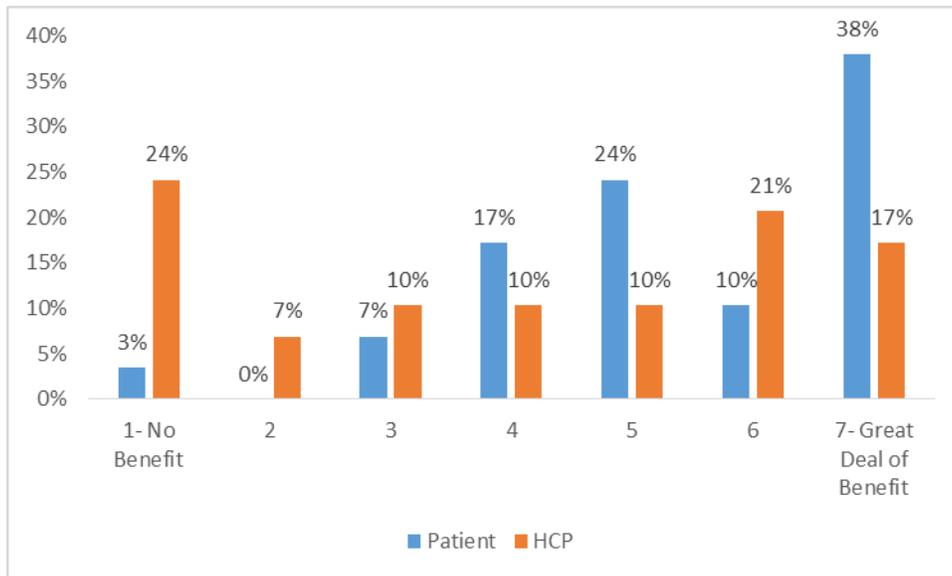
Figure 6.22. Cancer (N=22): Perceived Benefit



Seizures

Figure 6.23 shows benefit scores reported by patients and their certifying HCPs for seizure patients for whom both scores were available (n=29). Comparison of proportions of patients and HCPs reporting each benefit score shows that generally patients report higher degrees of benefit than HCPs: 38% of patients versus 17% of HCPs report scores of 6 or 7; 3% of patients versus 24% HCPs report no benefit.

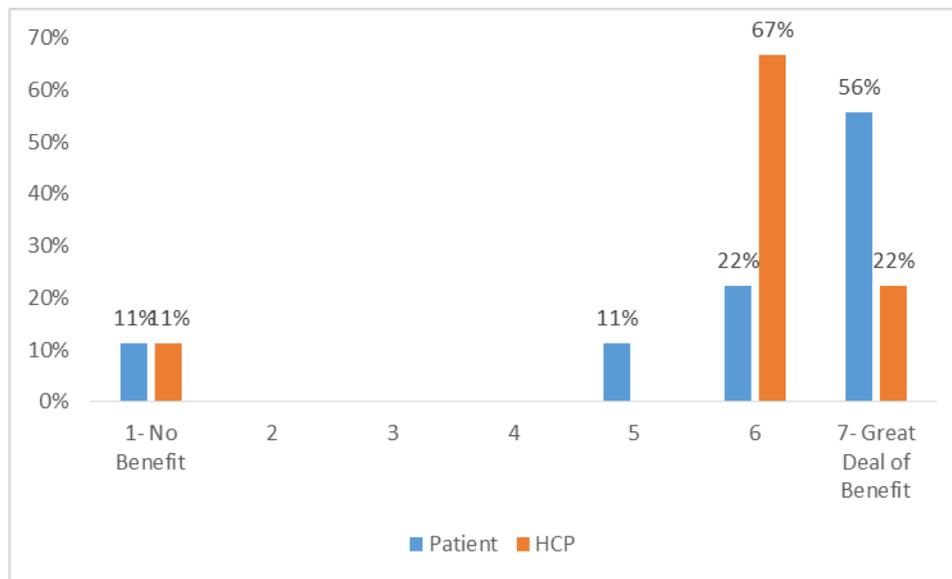
Figure 6.23. Seizures (N=29): Perceived Benefit



Crohn's Disease

Figure 6.24 shows benefit scores reported by patients and their certifying HCPs for Crohn's disease patients for whom both scores were available (n=9). Comparison of proportions of patients and HCPs reporting each benefit score shows general agreement about degree of benefit experienced: 89% of patients and 78% of HCPs report scores of 6 or 7; 11% of both patients and HCPs report scores of 1.

Figure 6.24. Crohn's Disease (N=9): Perceived Benefit



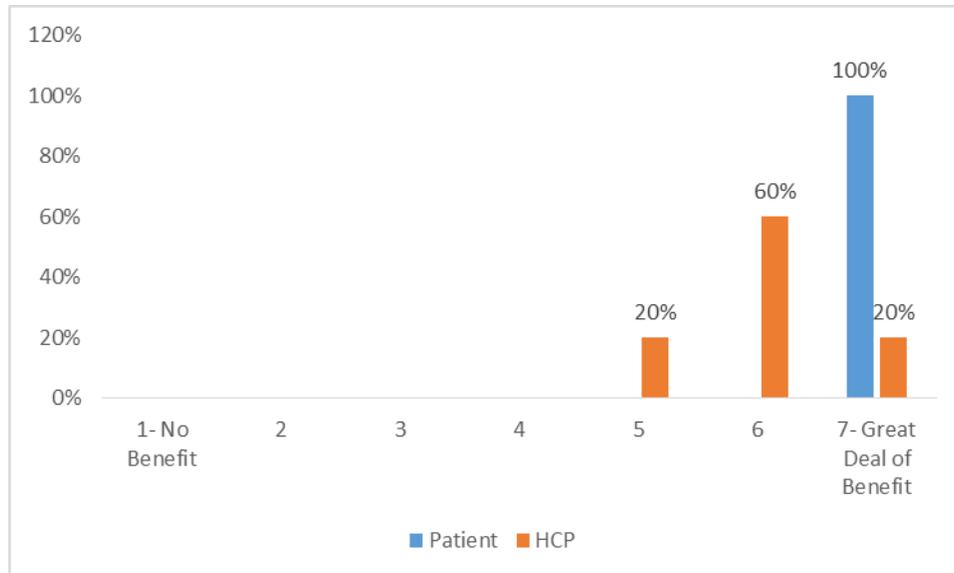
Terminal Illness

No patients with terminal illness had both an HCP-submitted survey and patient-submitted survey.

HIV/AIDS

Figure 6.25 shows benefit scores reported by patients and their certifying HCPs for HIV/AIDS patients for whom both scores were available (n=5). Comparison of proportions of patients and HCPs reporting each benefit score shows general agreement about degree of benefit experienced: 100% of patients and 80% of HCPs report scores of 6 or 7.

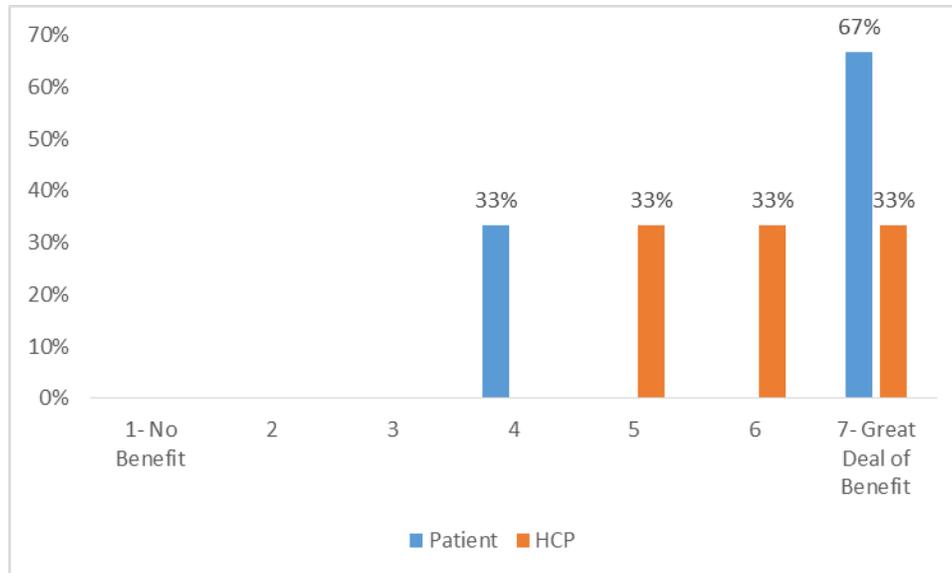
Figure 6.25. HIV/AIDS (N=5): Perceived Benefit



Tourette Syndrome

Figure 6.26 shows benefit scores reported by patients and their certifying HCPs for Tourette syndrome patients for whom both scores were available (n=3). Comparison of proportions of patients and HCPs reporting each benefit score shows general agreement about degree of benefit experienced: 67% of patients and 67% of HCPs report scores of 6 or 7.

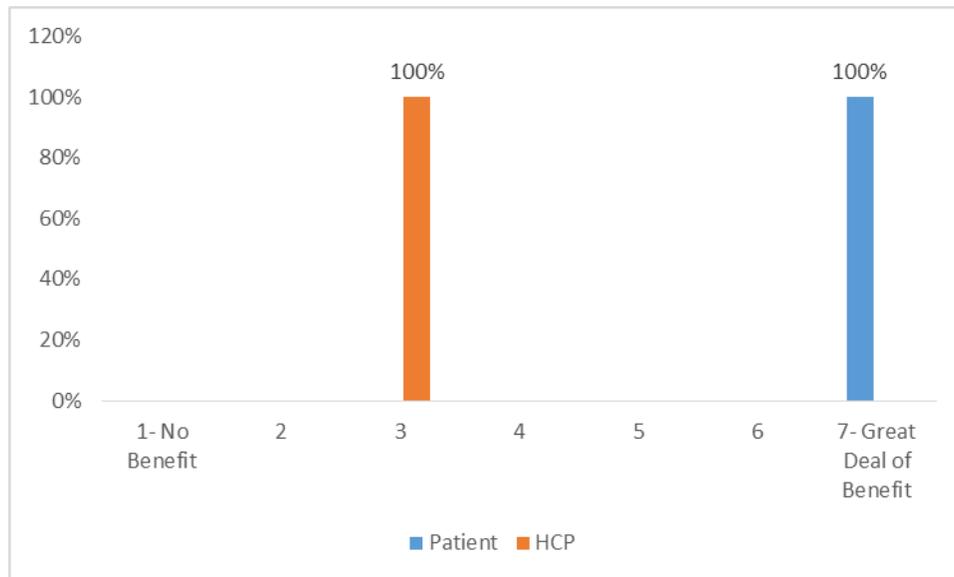
Figure 6.26. Tourette Syndrome (N=3): Perceived Benefit



Glaucoma

Figure 6.27 shows the benefit scores reported for one glaucoma patient who completed a survey (reported benefit score of 7) and whose HCP also completed a survey (reported benefit score of 3).

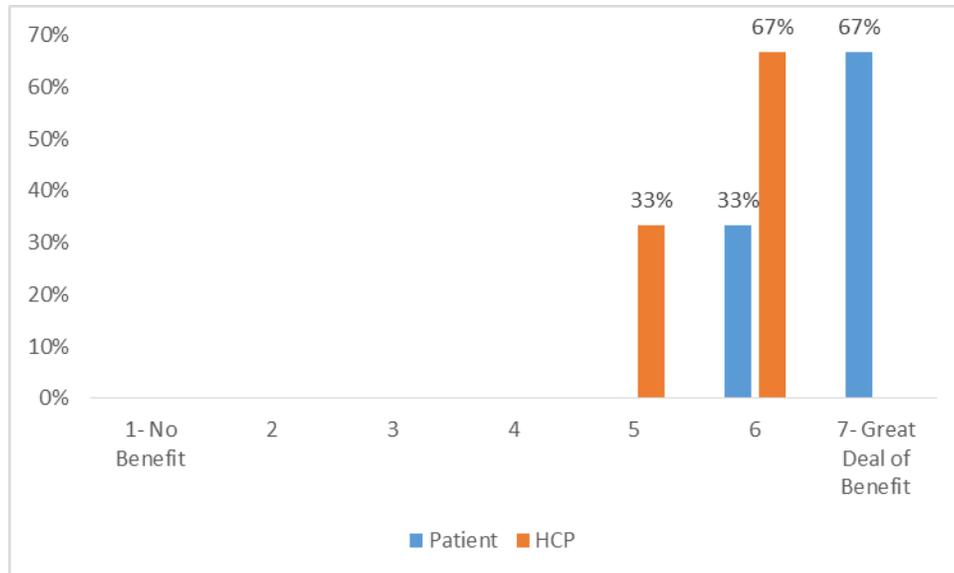
Figure 6.27. Glaucoma (N=1): Perceived Benefit



ALS

Figure 6.28 shows benefit scores reported by patients and their certifying HCPs for ALS patients for whom both scores were available (n=3). Comparison of proportions of patients and HCPs reporting each benefit score shows general agreement about degree of benefit experienced: 100% of patients and 67% of HCPs report scores of 6 or 7.

Figure 6.28. ALS (N=3): Perceived Benefit



Benefits Reported on Surveys: Conclusions

Of 1491 patients making a purchase in the first program year, 53% completed a survey three months after the first purchase. Among respondents, 43% reported experiencing the highest degree of benefit from medical cannabis and 87% reported at least a moderate degree of benefit (score of 4 or greater on a 1 to 7 scale). Patients reported the types of benefits experienced, which were predominantly (64%) various types of symptom improvement; many patients (25%) also reported global health benefits as the most important benefits from medical cannabis.

For patients making a purchase in the first six months of the program (n=774), 32% of HCP surveys were submitted. Overall, HCP reports of benefit were more conservative than those of patients, but 20% reported that the patient experienced the highest degree of benefit from medical cannabis and 60% reported at least a moderate degree of benefit. Among patients purchasing in the first six program months, 126 patients had both patient and HCP surveys completed and comparison of benefit scores indicated general agreement between the two scores for most patients.

Benefits Reported on the Patient Self-Evaluation

The Patient Self-Evaluation (PSE) contains questions that allow the Office of Medical Cannabis (OMC) to look for improvements in symptoms over time. Patients are required to complete a PSE prior to each medical cannabis purchase (including before their first medical cannabis purchase). This allows for capture of the patients’ symptoms at baseline – prior to taking any medical cannabis, as well as prior to each subsequent medical cannabis purchase. Hence, symptom change over time can be analyzed during the patients’ participation in the program.

All patients received a standard set of 8 symptom measures on the PSE. In addition, some patients received additional symptom questions depending on their qualifying medical condition(s). These two sets of symptom measures will be subsequently discussed below. Data from the PSE were extracted from patients who enrolled during the first program year (enrolled between July 1, 2015 and June 30, 2016; 1660 patients enrolled during this time period).

Standard 8 Symptom Measures

The standard 8 symptom measures that all patients received are answered on a 0-10 numerical rating scale (NRS), with 0 indicating absence of the symptom to 10 indicating that the symptom is as bad as the patient can imagine (see Box 6.1). Therefore, higher scores on these measures indicate poorer management of these symptoms. Patients are asked to rate symptom severity over the past 24 hours.

Box 6.1. Listing of the Standard 8 symptom measures that all patients answer, including the responses options available to patients.

<u>Standard 8 Symptom Measures:</u>											
Anxiety									Fatigue		
Lack of Appetite									Nausea		
Depression									Pain		
Disturbed Sleep									Vomiting		
<u>Response Options (0 – 10 NRS):</u>											
	0	1	2	3	4	5	6	7	8	9	10
Symptom not present											Symptom as bad as one can image

To understand whether patients derived any symptom benefits during their participation in the program, the following three questions were explored for each Standard 8 symptom measure:

QUESTION 1

Of those patients who experienced moderate to severe symptoms at baseline (score of 4 or higher at baseline), what percentage of them experienced at least a 30% improvement in symptoms within four months of their first medical cannabis purchase? The threshold of $\geq 30\%$ reduction on a 0-10 point scale was chosen because this threshold has been documented in clinical trials to represent clinically meaningful change – especially for pain reduction and spasticity reduction. Examples of $\geq 30\%$ change include moving from a score of 10 to a score of 7, from 9 to 6, from 8 to 5, from 7 to 4, etc.

QUESTION 2

If a patient achieved at least a 30% improvement on symptoms within 4 months of their first medical cannabis purchase (determined in Question 1), what percentage of them will, on average, still maintain that level of improvement in the four months following that initial 30% symptom improvement? [Four-month follow-up period]

QUESTION 3

What medical cannabis products were purchased just *prior* to the patient’s initial report of symptom improvement (first time patient indicated $\geq 30\%$ improvement on the PSE)? What was the average daily intake of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) for these product types?

To address Question 1 the following procedure was adopted for each standard 8 measure: all patients who scored 4 or higher at baseline were identified as those experiencing moderate to severe symptoms, and all standard 8 responses that were submitted within 4 months of their first medical cannabis purchase were retained. From this dataset, each patient’s standard 8 responses were compared to their baseline response over time. The first instance a patient achieved at least a 30% symptom improvement was recorded, effectively demonstrating when – during the first 4 months following their first medical cannabis purchase – the patient achieved symptom improvement, if at all.

Calculating the percentage of patients who achieved $\geq 30\%$ symptom improvement within 4 months of their first medical cannabis purchase (Question 1) was done in two ways. In one method, the number of patients who achieved $\geq 30\%$ symptom improvement within 4 months was divided by the total number of patients that ever made a first purchase (patients with baseline PSE data). In the other method, the number of patients achieving $\geq 30\%$ symptom improvement within 4 months was divided by patients who had submitted additional PSE data (beyond their baseline response) within 4 months of their first purchase. The denominator in

the former method includes all patients who made a first purchase (all patients with a baseline PSE submission), while the latter method effectively restricts the denominator to those patients who submitted additional PSE symptom data following their baseline submission and within 4 months of their first purchase. Therefore, the former method allows for a more conservative estimation of symptom benefit. In the text of this report, we present results using the former, more conservative estimate of benefit. Those who made no additional purchases after their first purchase may have discontinued use because of lack of effectiveness, though they may have discontinued use for other reasons as well (i.e., medical cannabis cost, side effects, etc.).

Since Question 1 examines symptom improvement within 4 months of their first medical cannabis purchase, patients who had not been enrolled in the program for at least 4 months since their first medical cannabis purchase were not included in the analysis. When PSE data were extracted in late December 2016, 1512 patients from the first year cohort (91.1% of the 1st year cohort) had been enrolled for at least 4 months since their first medical cannabis purchase—results on the standard 8 symptom measures are reported on this cohort subset.

Question 2 was addressed by observing all symptom responses in the four months *following* the time point when the patient first achieved $\geq 30\%$ symptom improvement. For each patient, all symptom responses identified during those follow-up four months were averaged together. Patients who, on average, still maintained at least a 30% symptom improvement from baseline were identified as those showing persistence in their symptom benefits.

For Question 3, products that were purchased just *prior* to each patient's initial $\geq 30\%$ symptom improvement were identified and categorized by their THC/CBD ratio and intended route of administration (ROA). See Box 6.2 for definitions of these categories.

Box 6.2. Categories to describe medical cannabis products purchased by patients.

Medical Cannabis Products Categorized by THC:CBD Content Ratio:

- **Very High THC to CBD** = 100:1 or higher
- **High THC to CBD** = >4:1 up to 99:1
- **Balanced** = 1:1 up to 4:1
- **High CBD to THC** = \geq 1:1 up to 99:1
- **Very High CBD to THC** = 100:1 or higher

Product Routes of Administration (ROA):

- **Enteral:** for absorption through the gastrointestinal tract (includes capsules and oral solutions to swallow).
- **Inhalation:** for absorption through the lungs (includes products for vaporization)
- **Oromucosal:** for absorption through the oral mucosa (includes sublingual sprays and tinctures to hold in the mouth)

Overall Results on Standard 8 Symptom Measures

Data on the Standard 8 symptom measures were first analyzed across all patients regardless of their qualifying condition(s) and are displayed in Table 6.14 (n = 1512). The third and fourth column respectively display the number and percentage of patients (out of 1512 patients) experiencing moderate to severe symptoms at baseline (baseline response \geq 4) on a given Standard 8 measure. With the exception of vomiting, the responses from patients indicated a high degree of burden on all symptom measures at baseline (~60-90% patients indicated moderate to severe symptoms).

The fifth column in Table 6.14 shows the percentage and number of patients (out of those reporting at moderate to severe levels at baseline) who had achieved at least a 30% symptom improvement at any time within 4 months of their first medical cannabis purchase. Anywhere from 36% to 60% of patients reported achieving at least a 30% improvement in symptoms within 4 months of their first medical cannabis purchase. Improvements in pain and fatigue were the least likely to reach \geq 30% improvement in patients (respectively at 36.3% and 40.2%), with the greatest proportion of patients reaching \geq 30% improvement in nausea (55.6%), depression (56.8%), and vomiting (60.2%).

The number of patients who had symptom data in the 4-month period *following* their initial \geq 30% symptom improvement are listed in the sixth column in Table 6.14. All symptom responses during this time period were averaged together within each patient. The seventh column shows the percentage and number of patients who had achieved \geq 30% symptom improvement that had – on average – maintained at least that level of improvement in the 4-

month follow-up period. Roughly a half to two-thirds of the patients who achieved at least 30% symptom improvement had maintained it in the following 4 months. Lastly, the right-most column shows the percentage of all patients who both achieved and maintained at least a 30% symptom improvement in the 4-month follow-up period. For the majority of all symptoms, roughly a third of all patients experiencing moderate to severe symptoms will both achieve and maintain at least a 30% improvement in symptoms for at least 4 months.

For a more detailed look on overall results from the eight standard symptom measures, please refer to *Appendix D: Symptom Results from the Patient Self-Evaluation*. This Appendix shows the following for each Standard 8 measure: 1) a figure showing the distribution of patient responses at baseline, 2) a figure showing the cumulative percentage of patients achieving at least 30% symptom improvement at 2 weeks, 1 month, 2 months, 3 months, and 4 months (the denominator is different between the orange and blue bars; orange bars include all moderate to severe scoring patients at baseline while blue bars restrict analyses to only those patients who submitted data by the time point indicated on the x-axis), and 3) a figure showing the frequency distribution of patients by the average symptom change (%) each patient experienced in the 4-month follow-up period since they initially achieved $\geq 30\%$ symptom reduction.

Table 6.14. Overall standard 8 symptom results.

Condition	Standard 8 Symptom Measure	# of Patients Reporting at Moderate to Severe Levels at Baseline	% of Patients Reporting at Moderate to Severe Levels at Baseline	% of Patients Achieving $\geq 30\%$ Symptom Improvement within 4 months of First Purchase out of all Moderate to Severe Baseline Scorers (n)	# of Patients with Data in 4-mo Period Following Initial $\geq 30\%$ Symptom Improvement	% of Patients Who Achieved $\geq 30\%$ Symptom Improvement that Maintained it for at Least 4 months (n)	% of Patients that Both Achieved $\geq 30\%$ Symptom Improvement and Retained that Degree of Improvement for at Least 4 months
All Patients - Collapsed Across Conditions (n = 1512)	Anxiety	1185	78.4	53.8 (638)	460	53.1 (339)	28.6
	Appetite Lack	963	63.7	53.7 (517)	383	57.1 (295)	30.6
	Depression	1000	66.1	56.8 (568)	419	56.7 (322)	32.2
	Disturbed Sleep	1323	87.5	50.3 (665)	519	52.0 (346)	26.2
	Fatigue	1381	91.3	40.2 (555)	415	48.6 (270)	19.6
	Nausea	864	57.1	55.6 (480)	362	59.2 (284)	32.9
	Pain	1312	86.8	36.3 (476)	329	45.0 (214)	16.3
	Vomiting	480	31.7	60.2 (289)	213	57.8 (167)	34.8

Results on Standard 8 Symptom Measures Stratified by Qualifying Condition

Data on the Standard 8 symptom measures were also analyzed separately by qualifying condition. Results are presented in Table 6.15 below. The first column indicates the qualifying condition and the total number of patients who had been enrolled in the program for at least 4 months since their first medical cannabis purchase. For some conditions, results are further broken down by condition subcategories (i.e., breakdown cancer patients based on whether their certifying condition was accompanied by pain, nausea/vomiting, etc.); condition subcategories are preceded by a star (*). The third and fourth columns in Table 6.15 indicate the number and percentage of patients who experienced moderate to severe symptoms (score ≥ 4) at baseline for each symptom.

The fifth column in Table 6.15 indicates the percentage and number of patients (out of those reporting at moderate to severe levels at baseline) that had achieved at least a 30% symptom improvement at any time within 4 months of their first medical cannabis purchase. The number of patients who had symptom data in the 4-month period *following* their initial $\geq 30\%$ symptom improvement are listed in the sixth column in Table 6.15. All symptom responses submitted during this time period were averaged together within each patient. The seventh column shows the percentage and number of patients that had achieved at least a 30% symptom improvement that had subsequently maintained it, on average, for at least 4 months. Lastly, the right-most column shows the percentage of all patients that had both achieved and maintained at least a 30% symptom improvement for at least 4 months.

Results generally show a high degree of burden for these eight symptoms at baseline. The instances where symptom severity is noticeably lower tend to be as expected; for example, nausea and vomiting in patients with Tourette syndrome and in patients with glaucoma. Among baseline responses to the eight symptom measures, those with the highest proportion rated as moderate to severe (score ≥ 4) include fatigue, disturbed sleep, pain, and anxiety. For each of the medical conditions, a substantial proportion of patients achieved $\geq 30\%$ reduction in most of the eight symptoms. Improvement was generally a bit higher in patients with seizures and with Tourette Syndrome and a bit lower in patients with cancer. Overall, a smaller proportion of patients achieved $\geq 30\%$ reduction of pain and fatigue and a higher proportion of patients achieved $\geq 30\%$ improvement in appetite and reduction in vomiting. For each medical condition, roughly half to three-quarters of the patients who experienced a $\geq 30\%$ reduction in a particular symptom within the first four months maintained that level of improvement over the following four months.

Table 6.15. Standard 8 symptom results stratified by qualifying condition.

Condition	Standard 8 Symptom Measure	# of Patients Reporting at Moderate to Severe Levels at Baseline	% of Patients Reporting at Moderate to Severe Levels at Baseline	% of Patients Achieving ≥30 Symptom Improvement within 4 months of First Purchase (n)	# of Patients with Data in 4-mo Period Following Initial ≥30% Symptom Improvement	% of Patients Who Achieved ≥30% Symptom Improvement that Maintained it for at Least 4 months (n)	% of Patients that Both Achieved ≥30% Symptom Improvement and Retained that Degree of Improvement for at Least 4 months
Muscle Spasms (n = 667)	Anxiety	553	82.9	54.8 (303)	250	60.7 (184)	33.3
	Appetite Lack	407	61.0	58.2 (237)	198	65.0 (154)	37.8
	Depression	471	70.6	58.0 (273)	227	63.0 (172)	36.5
	Disturbed Sleep	604	90.6	49.7 (300)	265	61.7 (185)	30.6
	Fatigue	624	93.6	42.0 (262)	227	55.3 (145)	23.2
	Nausea	366	54.9	63.1 (231)	195	65.4 (151)	41.3
	Pain	640	96.0	33.8 (216)	188	51.4 (111)	17.3
	Vomiting	192	28.8	65.1 (125)	103	66.4 (83)	43.2
Cancer (n = 405)	Anxiety	309	76.3	45.0 (139)	112	56.1 (78)	25.2
	Appetite Lack	321	79.3	39.3 (126)	102	57.1 (72)	22.4
	Depression	274	67.7	48.5 (133)	101	55.6 (74)	27.0
	Disturbed Sleep	355	87.7	42.0 (149)	122	47.0 (70)	19.7
	Fatigue	384	94.8	25.3 (97)	83	41.2 (40)	10.4
	Nausea	283	69.9	38.2 (108)	85	60.2 (65)	23.0
	Pain	356	87.9	28.9 (103)	80	40.8 (42)	11.8
	Vomiting	168	41.5	47.6 (80)	64	57.5 (46)	27.4
*Cancer: Pain (n = 285)	Pain	268	94.0	31.0 (83)	64	41.0 (34)	12.7
*Cancer: Nausea/Vomiting (n = 235)	Appetite Lack	200	85.1	41.0 (82)	66	57.3 (47)	23.5
	Nausea	184	78.3	34.8 (64)	49	54.7 (35)	19.0
	Vomiting	113	48.1	44.2 (50)	39	52.0 (26)	23.0
*Cancer: Cachexia/Wasting (n = 147)	Appetite Lack	124	84.4	38.7 (48)	39	58.3 (28)	22.6
Seizures (n = 299)	Anxiety	202	67.6	67.3 (136)	120	71.3 (97)	48.0
	Appetite Lack	145	48.5	76.6 (111)	97	73.9 (82)	56.6
	Depression	158	52.8	73.4 (116)	101	74.1 (86)	54.4
	Disturbed Sleep	242	80.9	69.0 (167)	155	63.5 (106)	43.8
	Fatigue	246	82.3	61.8 (152)	143	64.5 (98)	39.8
	Nausea	138	46.2	72.5 (100)	93	79.0 (79)	57.2
	Pain	190	63.5	60.0 (114)	106	69.3 (79)	41.6
	Vomiting	90	30.1	80.0 (72)	66	79.2 (57)	63.3

Table 6.15 Continued. Standard 8 symptom measures.

Condition	Standard 8 Symptom Measure	# of Patients Reporting at Moderate to Severe Levels at Baseline	% of Patients Reporting at Moderate to Severe Levels at Baseline	% of Patients Achieving ≥30 Symptom Improvement within 4 months of First Purchase (n)	# of Patients with Data in 4-mo Period Following Initial ≥30% Symptom Improvement	% of Patients Who Achieved ≥30% Symptom Improvement that Maintained it for at Least 4 months (n)	% of Patients that Both Achieved ≥30% Symptom Improvement and Retained that Degree of Improvement for at Least 4 months
Crohn's Disease (n = 102)	Anxiety	87	85.3	57.5 (50)	43	54.0 (27)	31.0
	Appetite Lack	80	78.4	53.8 (43)	37	58.1 (25)	31.3
	Depression	68	66.7	51.5 (35)	31	65.7 (23)	33.8
	Disturbed Sleep	89	87.3	42.7 (38)	37	65.8 (25)	28.1
	Fatigue	96	94.1	36.5 (35)	31	48.6 (17)	17.7
	Nausea	72	70.6	65.3 (47)	31	59.6 (28)	38.9
	Pain	97	95.1	41.2 (40)	32	47.5 (19)	19.6
	Vomiting	31	30.4	54.8 (17)	16	82.4 (14)	45.2
Terminal Illness (n = 81)	Anxiety	60	74.1	51.7 (31)	28	58.1 (18)	30.0
	Appetite Lack	64	79.0	37.5 (24)	19	45.8 (11)	17.2
	Depression	54	66.7	48.1 (26)	22	61.5 (16)	29.6
	Disturbed Sleep	65	80.2	44.6 (29)	28	55.2 (16)	24.6
	Fatigue	76	93.8	21.1 (16)	14	37.5 (6)	7.9
	Nausea	56	69.1	44.6 (25)	23	64.0 (16)	28.6
	Pain	72	88.9	19.4 (14)	11	50.0 (7)	9.7
	Vomiting	35	43.2	57.1 (20)	18	50.0 (10)	28.6
*Terminal Illness: Pain (n = 57)	Pain	54	94.7	20.4 (11)	8	45.5 (5)	9.3
*Terminal Illness: Nausea/Vomiting (n = 36)	Appetite Lack	31	86.1	41.9 (13)	11	61.5 (8)	25.8
	Nausea	28	77.8	35.7 (10)	10	70.0 (7)	25.0
	Vomiting	18	50.0	50.0 (9)	8	44.4 (4)	22.2
*Terminal Illness: Cachexia/Wasting (n = 29)	Appetite Lack	23	79.3	43.5 (10)	9	60.0 (6)	26.1
HIV/AIDS (n = 48)	Anxiety	44	91.7	50.0 (22)	20	68.2 (15)	34.1
	Appetite Lack	39	81.3	48.7 (19)	17	63.2 (12)	30.8
	Depression	34	70.8	47.1 (16)	15	75.0 (12)	35.3
	Disturbed Sleep	44	91.7	50.0 (22)	18	50.0 (11)	25.0
	Fatigue	41	85.4	46.3 (19)	15	47.4 (9)	22.0
	Nausea	33	68.8	60.6 (20)	17	65.0 (13)	39.4
	Pain	45	93.8	40.0 (18)	14	50.0 (9)	20.0
	Vomiting	20	41.7	50.0 (10)	9	80.0 (8)	40.0

Table 6.15 Continued. Standard 8 symptom measures.

Condition	Standard 8 Symptom Measure	# of Patients Reporting at Moderate to Severe Levels at Baseline	% of Patients Reporting at Moderate to Severe Levels at Baseline	% of Patients Achieving ≥30 Symptom Improvement within 4 months of First Purchase (n)	# of Patients with Data in 4-mo Period Following Initial ≥30% Symptom Improvement	% of Patients Who Achieved ≥30% Symptom Improvement that Maintained it for at Least 4 months (n)	% of Patients that Both Achieved ≥30% Symptom Improvement and Retained that Degree of Improvement for at Least 4 months
Tourette Syndrome (n = 28)	Anxiety	26	92.9	69.2 (18)	17	72.2 (13)	50.0
	Appetite Lack	8	28.6	50.0 (4)	3	75.0 (3)	37.5
	Depression	20	71.4	75.0 (15)	14	86.7 (13)	65.0
	Disturbed Sleep	21	75.0	76.2 (16)	16	75.0 (12)	57.1
	Fatigue	21	75.0	66.7 (14)	13	50.0 (7)	33.3
	Nausea	5	17.9	100.0 (5)	5	80.0 (4)	80.0
	Pain	17	60.7	64.7 (11)	11	90.9 (10)	58.8
	Vomiting	1	3.6	100.0 (1)	1	100.0 (1)	100.0
Glaucoma (n = 21)	Anxiety	14	66.7	42.9 (6)	6	50.0 (3)	21.4
	Appetite Lack	7	33.3	85.7 (6)	5	66.7 (4)	57.1
	Depression	14	66.7	85.7 (12)	11	58.3 (7)	50.0
	Disturbed Sleep	18	85.7	61.1 (11)	10	54.5 (6)	33.3
	Fatigue	19	90.5	42.1 (8)	7	37.5 (3)	15.8
	Nausea	6	28.6	16.7 (1)	1	100.0 (1)	16.7
	Pain	18	85.7	33.3 (6)	6	50.0 (3)	16.7
	Vomiting	1	4.8	0.0 (0)	0	-- (0)	0.0
ALS (n = 21)	Anxiety	17	81.0	52.9 (9)	7	55.6 (5)	29.4
	Appetite Lack	8	38.1	87.5 (7)	5	57.1 (4)	50.0
	Depression	15	71.4	40.0 (6)	5	50.0 (3)	20.0
	Disturbed Sleep	18	85.7	33.3 (6)	6	83.3 (5)	27.8
	Fatigue	20	95.2	35.0 (7)	7	71.4 (5)	25.0
	Nausea	9	42.9	55.6 (5)	4	80.0 (4)	44.4
	Pain	17	81.0	47.1 (8)	7	25.0 (2)	11.8
	Vomiting	2	9.5	50.0 (1)	1	100.0 (1)	50.0

Appendix D: Symptom Results from the Patient Self-Evaluation shows the following for each Standard 8 measure stratified by qualifying medical condition: 1) a figure showing the distribution of patient responses at baseline, 2) a figure showing the cumulative percentage of patients achieving at least 30% symptom improvement at 2 weeks, 1 month, 2 months, 3 months, and 4 months (the denominator is different between the orange and blue bars; orange bars include all moderate to severe scoring patients at baseline while blue bars restrict analyses to only those patients who submitted data by the time point indicated on the x-axis), 3) a figure showing the frequency distribution of patients by the average symptom change (%) each patient experienced in the 4-month follow-up period since they initially achieved $\geq 30\%$ symptom reduction, and 4) a table of medical cannabis products patients purchased just prior to achieving $\geq 30\%$ symptom improvement for the first time, along with the average daily THC and CBD dose taken by patients.

Medical cannabis products that were purchased just prior to the initial 30% symptom improvement are discussed only briefly in this section (Question 3), and the reader is encouraged to see *Appendix D: Symptom Results from the Patient Self-Evaluation* for the full table of results. Here, only a few results regarding medical cannabis purchases are discussed as examples—some in relation to improvements on a particular Standard 8 measure, and others in relation to a particular condition-specific symptom measure.

Table 6.16 below shows the most common medical cannabis products that were purchased by cancer patients just prior to achieving the initial 30% reduction in nausea symptoms. The second column from the right indicates the number of patients who purchased specific products just prior to that initial symptom reduction (products purchased indicated by “X”s). The table also shows the average daily amount of THC and CBD (mg) patients consumed (right-most column), which was derived from manufacturer-supplied product information and pharmacist-entered calculations of how long the purchased supply would last. Very High THC:CBD vaporization products were purchased most frequently (n = 20), followed by a combination of Very High THC:CBD enteral products and Very High THC:CBD vaporization products (n = 12). See *Appendix D: Symptom Results from the Patient Self-Evaluation* for full results.

Table 6.16. Top 5 medical cannabis product(s) purchased by cancer patients just prior to achieving the initial 30% reduction in the Standard 8 nausea measure.

Very High THC to CBD	Enteral				Inhalation				Oromucosal				% of Patients out of 109 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)		
	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	High THC to CBD	High THC to CBD	Balanced			High CBD to THC	Very High CBD to THC
					X										18.3 (20)	55.9 mg/0.4 mg
X					X										11.0 (12)	71.6 mg/0.5 mg
										X					8.3 (9)	86.3 mg/0.4 mg
		X													6.4 (7)	135.5 mg/83.2 mg
X		X			X			X							4.6 (5)	61.4 mg/15.6 mg

Table 6.17 below shows the most common medical cannabis products that were purchased by terminal illness patients just prior to achieving the initial 30% reduction in nausea symptoms. The most frequently purchased products were a combination of both Very High THC:CBD products for oral administration and vaporization (n = 3), followed by Balanced THC:CBD products for inhalation only (n = 3). See *Appendix D: Symptom Results from the Patient Self-Evaluation* for full results.

Table 6.17. Top 7 medical cannabis product(s) purchased by terminal illness patients just prior to achieving the initial 30% reduction in the Standard 8 nausea measure.

Enteral			Inhalation			Oromucosal			% of Patients out of 26 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	Very High CBD to THC	High CBD to THC	Balanced	Very High THC to CBD	High THC to CBD	Balanced		
X						X			11.5 (3)	67.1 mg/0.5 mg
						X			11.5 (3)	44.5 mg/0.4 mg
X		X				X			7.7 (2)	45.5 mg/37.5 mg
		X			X				7.7 (2)	110.1 mg/5.9 mg
		X						X	7.7 (2)	78.6 mg/61.1 mg
		X							7.7 (2)	49.0 mg/46.0 mg
			X						7.7 (2)	4.4 mg/206.7 mg

Table 6.18 below shows the most common medical cannabis products purchased by HIV/AIDS patients just prior to their initial 30% reduction in pain symptoms. Balanced THC:CBD products were purchased most frequently (n = 6), followed by Very High THC:CBD products for inhalation (n = 3). See *Appendix D: Symptom Results from the Patient Self-Evaluation* for full results.

Table 6.18. Top 4 medical cannabis product(s) purchased by HIV/AIDS patients just prior to achieving the initial 30% reduction in the Standard 8 pain measure.

Enteral			Inhalation			Oromucosal			% of Patients out of 18 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	Very High CBD to THC	High CBD to THC	Balanced	Very High THC to CBD	High THC to CBD	Balanced		
		X							33.3 (6)	23.1 mg/22.1 mg
			X						16.7 (3)	65.2 mg/0.3 mg
X		X							11.1 (2)	5.0 mg/0.0 mg
			X		X				11.1 (2)	51.7 mg/18.2 mg

Condition-Specific Symptom Measures

In addition to the Standard 8 measures, some patients received additional symptom questions on the PSE to more adequately address condition-specific symptoms. These include, among others, questions on seizure frequency for seizure patients, questions on spasm frequency for muscle spasm and ALS patients, and Crohn’s activity in Crohn’s patients. While patients received the same response options on the Standard 8 measures (respond from 1-10 on a

numerical rating scale), response options for condition-specific measures varied and will be described in this section. All condition-specific measures were investigated within the same framework as the Standard 8 measures: 1) what percentage of patients achieved symptom improvement within the four months since their first medical cannabis purchase compared to their baseline responses, 2) what percentage of those achieving symptom improvement showed general persistence in the 4-month follow-up period, and 3) what medical cannabis products were purchased just prior to the patient reporting initial symptom improvements. A summary of results are similarly presented in a table like those presented for the Standard 8 measures (see Table 6.19 below).

The first column in Table 6.19 lists each condition that received additional symptom questions beyond the Standard 8. The second column briefly indicates the nature of these additional condition-specific symptom measures, with the number of patients included in the analysis at baseline indicated in the third column (baseline, meaning patients who provided data and met criteria on these measures at the beginning of the program – prior to purchasing any medical cannabis). The fourth column indicates the percentage and number of patients achieving a specified threshold of symptom improvement within four months of purchasing their first medical cannabis (denominator is patients included in the analysis at baseline). The threshold to determine symptom improvement for these analyses are subsequently described below, found in the descriptive section for each condition. The number of patients who had symptom data in the 4-month period following their initial symptom improvement are listed in the fifth column in Table 6.19. All symptom responses during this time period were averaged together within each patient. The sixth column indicates the percentage and number of patients who had achieved symptom improvement that subsequently still maintained that improvement for at least 4 months. Lastly, the right-most column shows the percentage of all patients who both achieved and maintained symptom improvements for at least 4 months. A more detailed discussion of these condition-specific results will follow Table 6.19.

Table 6.19. Condition-Specific Measures.

Condition	Condition-Specific Symptom Measure	# of Patients Included in Analysis	% of Patients Achieving Threshold Symptom Improvement within 4 months of First Purchase (n)	# of Patients with Data in 4-mo Period Following Initial Threshold Symptom Improvement	% of Patients Who Achieved Threshold Symptom Improvement that Maintained it for at Least 4 months (n)	% of Patients that Both Achieved Threshold Symptom Improvement and Retained that Degree of Improvement for at Least 4 months
Muscle Spasms	Weekly Spasms Frequency	629	48.0 (302)	225	57.6 (174)	27.6
	0-10 Spasticity Scale	618	36.4 (225)	197	47.1 (106)	17.2
Cancer: Nausea/Vomiting	Chemo-Induced Nausea	147	37.4 (55)	29	34.5 (19)	12.9
	Chemo-Induced Vomiting	77	41.6 (32)	20	56.3 (18)	23.4
Cancer: Cachexia/Wasting	Weight	147	13.6 (20)	15	45.0 (9)	6.1
Seizures	Weekly Seizure Frequency	262	68.3 (179)	150	70.9 (127)	48.5
Crohn's Disease	# Liquid Stools	41	51.2 (21)	17	57.1 (12)	29.3
	Abdominal Pain	73	53.4 (39)	29	35.9 (14)	19.2
	General Well-Being	15	46.7 (7)	5	28.6 (2)	13.3
	Measures Combined	102	51.0 (52)	41	42.3 (22)	21.6
	Weight	102	20.6 (21)	18	57.1 (12)	11.8
Terminal Illness: Cachexia/Wasting	Weight	29	20.7 (6)	5	50.0 (3)	10.3
HIV/AIDS	Weight	48	14.6 (7)	3	42.9 (3)	6.3
Tourette Syndrome	Weekly Tic Frequency	28	60.7 (17)	15	76.5 (13)	46.4
ALS	Weekly Spasms Frequency	18	33.3 (6)	4	66.7 (4)	22.2
	0-10 Spasticity Scale	15	20.0 (3)	3	100.0 (3)	20.0

Severe and Persistent Muscle Spasms

Patients with muscle spasms were given two questions to assess the severity of their muscle spasms. First, patients were given the option to respond to the number of muscle spasms they experienced the day before or the number of muscle spasms they experienced within the last week. These allowed for the calculation of weekly spasm frequency. Secondly, patients were asked to rate the severity of their muscle spasms on a 0-10 numerical rating scale (NRS), with 0 indicating absence of spasms to 10 indicating spasticity being as bad as the patient could imagine. For the analysis in Table 6.19 above, responses to the 0-10 spasticity measure were restricted to patients experiencing moderate to severe spasticity at baseline (score of 4 or higher), while all patients responding to the weekly spasms frequency question were included in the analysis. In the analysis of both measures, symptom improvement was defined as achieving at least a 30% reduction in symptoms (30% decrease in weekly spasm frequency; 30% decrease on the 0-10 NRS spasticity measure) compared to baseline.

Weekly spasm frequency was reduced by $\geq 30\%$ in nearly half (48.0%) of the muscle spasm patients. Among patients who achieved $\geq 30\%$ reduction, 58% (27.6% of patients included in analysis at baseline) retained that level of improvement over the next four months.

Severity of muscle spasticity was reduced by $\geq 30\%$ for 36.4% of the patients with moderate to severe muscle spasticity at baseline. Among patients who achieved $\geq 30\%$ reduction, 47% (17.2% of patients included in analysis at baseline) retained that level of improvement over the next four months.

Table 6.20 below shows the top 5 medical cannabis product types that were purchased by muscle spasm patients just prior to achieving $\geq 30\%$ weekly spasm reduction for the first time, including the number of patients who purchased those specific product types (second column from right). It also shows the average daily amount of THC and CBD (mg) patients consumed (right-most column), which was derived from manufacturer-derived product information and pharmacist-entered calculations of how long the purchased supply would last. Full purchasing details are in *Appendix D: Symptom Results from the Patient Self-Evaluation*. The most frequently purchased product types preceding the initial symptom improvement were a combination of Balanced THC:CBD products for oral administration and Balanced THC:CBD products for vaporization (n = 34), followed by Very High THC:CBD products for vaporization (n = 30).

Table 6.20. Top 5 medical cannabis product types purchased by muscle spasm patients just prior to achieving $\geq 30\%$ reduction in weekly spasms. Last column shows the average daily THC/CBD dose that was used by patients purchasing those product types (second column from right).

Enteral					Inhalation					Oromucosal					% of Patients out of 301 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
		X					X								11.3 (34)	55.3 mg/35.1 mg
					X										10.0 (30)	77.8 mg/0.5 mg
		X			X										9.6 (29)	79.6 mg/30.0 mg
		X													8.3 (25)	23.6 mg/22.4 mg
					X		X								7.0 (21)	99.8 mg/17.5 mg

Cancer: Nausea and Vomiting

Patients certified for cancer accompanied by severe and persistent nausea or vomiting were asked to assess the severity of chemotherapy-induced nausea and vomiting on a 0-10 numerical rating scale. Patients who experienced chemotherapy-induced nausea and vomiting at moderate to severe levels at baseline (score of 4 or higher) were included in the analysis in Table 6.19, with symptom improvement being defined as achieving at least a 30% improvement in symptoms (30% decrease on the 0-10 nausea/vomiting NRS) compared to baseline.

Severity of chemotherapy-induced nausea was reduced by $\geq 30\%$ for 37.4% of the patients with moderate to severe chemotherapy-induced nausea at baseline. Among the patients who achieved $\geq 30\%$ reduction, 35% (12.9% of patients included in analysis at baseline) retained that level of improvement over the next four months.

Severity of chemotherapy-induced vomiting was reduced by $\geq 30\%$ for 41.6% of the patients with moderate to severe chemotherapy-induced vomiting at baseline. Among the patients who achieved $\geq 30\%$ reduction, 56% (23.4% of patients included in analysis at baseline) retained that level of improvement over the next four months.

Cancer: Cachexia and Severe Wasting

Body weights were analyzed for patients certified for cancer accompanied by cachexia and/or severe wasting. Symptom improvement was defined as achieving at least a 3% increase in body weight compared to baseline weight.

An increase of at least 3% in body weight was reported by 13.6% of patients. Among the patients who achieved $\geq 3\%$ increase in body weight, 45% (6.1% of patients included in analysis at baseline) retained that increase over the next four months.

Seizures

Patients with seizures were given two questions to assess the severity of their seizures. First, patients were given the option to respond to the number of seizures they experienced the day before or the number of seizures they experienced within the last week. These allowed for the calculation of weekly spasm frequency. Table 6.19 shows results from the weekly seizure frequency measure, with symptom improvement defined as achieving at least a 30% improvement in symptoms (30% decrease in weekly seizure frequency) compared to baseline.

Weekly seizure frequency was reduced by $\geq 30\%$ in 68.3% of the seizure patients. Among patients who achieved $\geq 30\%$ reduction, 71% (48.5% of patients included in analysis at baseline) retained that level of improvement over the next four months.

Table 6.21 below shows the top 5 medical cannabis product types that were purchased by seizure patients just prior to achieving $\geq 30\%$ symptom improvement for the first time, including the number of patients who purchased those specific product types (second column from right). It also shows the average daily amount of THC and CBD (mg) patients consumed (right-most column), which was derived from manufacturer-derived product information and pharmacist-entered calculations of how long the purchased supply would last. Full purchasing details are in *Appendix D: Symptom Results from the Patient Self-Evaluation*. The most frequently purchased product types preceding the initial symptom improvement were skewed towards relatively high CBD:THC products, with preference for oral administration of these products.

Table 6.21. Top 5 medical cannabis product types purchased by seizure patients just prior to achieving ≥30% reduction in weekly seizures. Last column shows the average daily THC/CBD dose that was used by patients purchasing those product types (second column from right).

Enteral				Inhalation				Oromucosal				% of Patients out of 178 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
		X										48.3 (86)	7.6 mg/159.5 mg
										X		16.9 (30)	13.2 mg/407.4 mg
	X				X							4.5 (8)	56.0 mg/37.4 mg
		X	X									3.4 (6)	4.9 mg/282.5 mg
	X											2.8 (5)	19.3 mg/15.9 mg

Crohn's Disease

Three questions from the Harvey-Bradshaw Index (HBI), which measures Crohn's disease activity, were included on the PSE for Crohn's disease patients. These three questions addressed the following: 1) the number of liquid or soft stools experienced yesterday, 2) general well-being yesterday (response options: "Very well", "Slightly below par", "Poor", "Very poor", "Terrible"), and 3) abdominal pain yesterday (response options: "None", "Mild", "Moderate", "Severe"). Responses to these three questions were summed into a combined score for each patient (combined according to HBI scoring guidelines) as well as analyzed separately in Table 6.19. The three questions were selected from the HBI because they were patient-reported measures (versus clinician assessments). The HBI has been validated, but since only three questions from the HBI were used, the clinical significance of these aggregate and individual scores is unclear. Lastly, body weight data submitted through the PSE were analyzed and included in Table 6.19.

Patients who indicated they experienced five or more liquid/soft stools at baseline were included in the analysis, with symptom improvement defined as achieving at least a 30% reduction in liquid/soft stools. Patients who indicated their general well-being was "Very Poor" or "Terrible" at baseline were included in the well-being analysis, with symptom improvement defined as feeling "Slightly Below Par" or "Very Well". Patients who indicated they experienced "Moderate" or "Severe" abdominal pains were included in the abdominal pain analysis, with symptom improvement defined as experiencing "Mild" to "No" abdominal pain. For the combined Crohn's activity measure (combined score on the three HBI measures), symptom improvement was defined as those achieving at least a 30% symptom improvement (30% decrease in the combined score compared to baseline). Lastly, body weight improvement was defined as a 3% increase in body weight.

Number of liquid/soft stools per day decreased by $\geq 30\%$ for 51.2% of patients with at least five liquid/soft stools per day at baseline. Among patients who achieved $\geq 30\%$ reduction, 57% (29.3% of patients included in analysis at baseline) retained that level of improvement over the next four months.

Severity of abdominal pain improved for 53.4% of patients with moderate or severe abdominal pain at baseline. Among patients who reported an improvement in abdominal pain, 36% (19.2% of patients included in analysis at baseline) retained that improvement over the next four months.

General well-being improved for 46.7% of patients who described their baseline well-being as "Very Poor" or "Terrible" at baseline. Among patients who reported an improvement in general well-being, 29% (13.3% of patients included in analysis at baseline) retained that improvement over the next four months.

On the combined Crohn's activity measure (number of liquid/soft stools, abdominal pain, general well-being), 51.0% of Crohn's Disease patients achieved $\geq 30\%$ improvement. Among

patients who achieved $\geq 30\%$ reduction, 42% (21.6% of patients included in analysis at baseline) retained that level of improvement over the next four months.

An increase of at least 3% in body weight was reported by 20.6% of patients. Among the patients who achieved $\geq 3\%$ increase in body weight, 57% (11.8% of patients included in analysis at baseline) retained that increase over the next four months.

Terminal Illness

Body weight measures on the PSE were analyzed in patients certified for terminal illness: accompanied by cachexia or severe wasting. Symptom improvement was defined as a 3% increase in body weight from their baseline body weight.

An increase of at least 3% in body weight was reported by 20.7% of patients. Among the patients who achieved $\geq 3\%$ increase in body weight, 50% (10.3% of patients included in analysis at baseline) retained that increase over the next four months.

HIV/AIDS

Body weight measures on the PSE were analyzed in HIV/AIDS patients. Similar to all body weight measures of improvement discussed previously, symptom improvement was defined as a 3% increase in body weight compared to their baseline body weight.

An increase of at least 3% in body weight was reported by 14.6% of patients. Among the patients who achieved $\geq 3\%$ increase in body weight, 43% (6.3% of patients included in analysis at baseline) retained that increase over the next four months.

Tourette Syndrome

Patients with Tourette Syndrome were given two questions to assess the severity of their tics. First, patients were given the option to respond to the number of tics they experienced the day before or the number of tics they experienced within the last week. These allowed for the calculation of weekly tic frequency. For Table 6.19, weekly tic frequency was analyzed in all patients, with symptom improvement defined as a 30% improvement in symptoms (30% decrease in weekly tics compared to baseline).

Weekly tic frequency was reduced by $\geq 30\%$ in 60.7% of the Tourette Syndrome patients. Among patients who achieved $\geq 30\%$ reduction, 76% (46.4% of patients included in analysis at baseline) retained that level of improvement over the next four months.

Table 6.22 below shows the top 4 medical cannabis product types that were purchased by Tourette patients just prior to achieving $\geq 30\%$ symptom improvement for the first time, including the number of patients who purchased those specific product types (second column from right). It also shows the average daily amount of THC and CBD (mg) patients consumed (right-most column), which was derived from manufacturer-derived product information and pharmacist-entered calculations of how long the purchased supply would last. Full purchasing details are in *Appendix D: Symptom Results from the Patient Self-Evaluation*. The most frequently purchased product types preceding the initial symptom improvement were Very High THC:CBD oromucosal products (4 patients) and a combination of Balanced THC:CBD oral products and Very High THC:CBD oral products (2 patients)

Table 6.22. Top 4 medical cannabis product types purchased by Tourette patients just prior to achieving $\geq 30\%$ reduction in weekly tics. Last column shows the average daily THC/CBD dose that was used by patients purchasing those product types (second column from right).

Enteral			Inhalation			Oromucosal			% of Patients out of 17 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	Balanced	High CBD to THC	Very High THC to CBD	Balanced	High CBD to THC	Very High THC to CBD	Balanced	High CBD to THC		
						X			23.5 (4)	147.3 mg/0.7 mg
X	X								11.8 (2)	24.0 mg/15.0 mg
	X								11.8 (2)	11.5 mg/8.5 mg
			X						11.8 (2)	64.6 mg/0.2 mg

Glaucoma

Intraocular pressure results were collected on the PSE from Glaucoma patients and are presented in Table 6.23 for each of the 21 patients included in this analysis. At the first PSE (prior to first medical cannabis purchase) patients were asked to provide the date and results of the most recent intraocular pressure test. On subsequent PSEs patients were asked to provide the date and results of any intraocular pressure test done since submission of the last PSE.

Results for seven of the 21 patients (33%) suggest a decrease in intraocular pressure after initiation of medical cannabis: patients #4, 8, 9, 14, 16, 17, and 19. One of those seven did not show a decrease at 5 months, but did show a decrease at 9 months. Four of them had measurement results after the date of the result that indicated a decrease: patients #4, 16, 17, and 19. Of those four, three have results indicating persistence of reduction over several months. The fourth (#19) had a reduction in month 2 but returned toward pre-medical cannabis levels at month 4. More detailed study, including accessing medical record data, would be needed to confirm measurement results and to assess whether observed improvements could have been due to changes in glaucoma therapy other than medical cannabis use.

Table 6.23. Intraocular pressure test results (left eye/right eye) from glaucoma patients (n = 21). Test results are noted by the month they occurred prior to or after the patients' first medical cannabis purchase ("First Visit").

Patient	Before 1st Medical Cannabis Purchase							First Visit	After 1st Medical Cannabis Purchase										
	12-mo	11-mo	5-mo	4-mo	3-mo	2-mo	1-mo		1-mo	2-mo	3-mo	4-mo	5-mo	6-mo	7-mo	9-mo	10-mo	11-mo	13-mo
1		15 / 11											11 / 10		7 / 12				
2							20 / 17			17 / 14							18 / 16		
3							18 / 20		19 / 18			18 / 18		19 / 22	19 / 18				
4						26 / 28	26 / 28			18 / 18				18 / 16					
5							21 / 26												
6			20 / 20						20 / 20										
7							17 / 15												
8					34 / 30								33 / 33			26 / 24			
9							26 / 23		17 / 18										
10						30 / 30													
11			22 / 24	27 / 21	21 / 24														
12							12 / 10				12 / 12								
13							22 / 14		22 / 14										
14							9 / 26			8 / 12									
15						17 / 18			19 / 24										
16		22 / 20							16 / 16		17 / 17	16 / 16						18 / 19	
17							23 / 23		16 / 16	19 / 25		16 / 19	16 / 19			16 / 18			
18					10 / 12					12 / 15									
19							30 / 22			19 / 16		26 / 16							
20						17 / 19	19 / 17		19 / 17										
21							17 / 26		17 / 28		20 / 25				19 / 20				24 / 28

ALS

Patients with ALS were given two questions to assess the severity of their muscle spasms. First, patients were given the option to respond to the number of spasms they experienced the day before or the number of spasms they experienced within the last week. These allowed for the calculation of weekly spasm frequency. Table 6.19 presents results on weekly spasm frequency and spasm severity (0-10 NRS). For the spasticity scale measure, patients who experienced moderate to severe spasms at baseline (scored 4 or higher) were included in the analysis, with symptom improvement defined as achieving at least a 30% symptom improvement (30% decrease on the 0-10 NRS compared to baseline).

Weekly spasm frequency was reduced by $\geq 30\%$ in 33.3% of the ALS patients. Among patients who achieved $\geq 30\%$ reduction, 67% (22.2% of patients included in analysis at baseline) retained that level of improvement over the next four months.

Severity of muscle spasticity was reduced by $\geq 30\%$ for 20.0% of the ALS patients with moderate to severe muscle spasticity at baseline. Among the three patients who achieved $\geq 30\%$ reduction, all three retained that level of improvement over the next four months (20.0% of patients included in analysis at baseline).

Table 6.24 below shows the top 5 medical cannabis product types that were purchased by ALS patients just prior to achieving $\geq 30\%$ weekly spasm reduction for the first time, including the number of patients who purchased those specific product types (second column from right). It also shows the average daily amount of THC and CBD (mg) patients consumed (right-most column), which was derived from manufacturer-derived product information and pharmacist-entered calculations of how long the purchased supply would last. Full purchasing details are in *Appendix D: Symptom Results from the Patient Self-Evaluation*. The most frequently purchased product types preceding the initial symptom improvement were skewed towards balanced THC:CBD products and relatively high THC:CBD products.

Table 6.24. Top 5 medical cannabis product types purchased by ALS patients just prior to achieving $\geq 30\%$ reduction in weekly spasms. Last column shows the average daily THC/CBD dose that was used by patients purchasing those product types (second column from right).

Enteral			Inhalation			% of Patients out of 6 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	Very High THC to CBD	High THC to CBD	Balanced		
		X				33.3 (2)	12.8 mg/5.1 mg
X			X			16.7 (1)	59.8 mg/0.3 mg
	X	X	X		X	16.7 (1)	67.0 mg/6.0 mg
	X	X				16.7 (1)	37.5 mg/8.1 mg
			X			16.7 (1)	42.2 mg/0.3 mg

Benefits Reported on the Patient Self-Evaluation: Conclusions

Similar to survey results, the PSE also demonstrated improvements on symptoms in medical cannabis patients. Patients enrolling in the program initially report a high degree of symptom burden with anywhere from roughly 40-60% of patients reporting symptom improvements within the 4 month period following their first medical cannabis purchase. If patients experienced improvements in symptoms, roughly half to three-quarters of them maintained those levels of improvement in the 4-month period following their initial report of improvement.

There are some limitations on the PSE to consider when interpreting results. Firstly, there is no symptom data on patients who decide over time not to purchase medical cannabis any longer (or for extended periods of time). As discussed earlier, patients must complete a PSE prior to each medical cannabis purchase. If a patient stops purchasing medical cannabis, there will be a parallel pause in symptom data to understand whether there may have been a lack of symptom improvements to halt purchases. This is the reason for presenting many analyses on symptom improvements in the context of the initial baseline patient pool – regardless of whether they provided any subsequent symptom data or not. This allows for more of a conservative estimate of symptom benefit over time. A second limitation on the PSE has to do with the patient’s approach and conscientiousness in completing the PSE—all symptom measures are self-reported which involves cognitive resources and motivation for the patient to complete the surveys as accurately as possible.

7. Adverse Side Effects

Summary

This chapter provides insight into the frequency and severity of adverse (negative) side effects through three sources of information: the Patient Self-Evaluation completed by the patient prior to each medical cannabis purchase, patient and health care practitioner surveys, and adverse event reports to the two medical cannabis manufacturers.

The three information sources tell a similar story. Around 20-25% of enrolled patients report negative physical or mental side effects of some kind, with the majority – around 60% - reporting only one and 90% reporting 3 or fewer unique side effects. The vast majority of adverse side effects, around 90%, are mild to moderate in severity. An assessment of the 30 patients reporting severe side effects, meaning “interrupts usual daily activities,” found no apparent pattern in patient age, medical condition, or type of medical cannabis product used. Results reported in this chapter are generally similar to those reported in published clinical trials of cannabis and cannabinoids, though with a somewhat lower frequency of occurrence reported in the program. Fortunately, up to the present no serious adverse events (life threatening or requiring hospitalization) have been reported.

Some limitations of the data should be mentioned. For example, when the patient completes a Patient Self-Evaluation and has it reviewed in consultation with pharmacist staff, the completeness and accuracy of reported side effects (on the Patient Self-Evaluation) ultimately depend on the attention and good communication of the patient. Perhaps a more significant risk for under-reporting through Patient Self-Evaluation data is the situation when a patient has an intolerable side effect and decides to make no more purchases of medical cannabis. If the patient doesn't go to a cannabis patient center for another purchase, the patient doesn't fill out another Patient Self-Evaluation, so the side effect is not documented through this mechanism. From anecdotal report and survey responses, we know this does occur. However, inquiries made of patients who have discontinued medical cannabis purchasing suggests this does not happen often. Finally, a weakness of the survey data is that many responders did not complete the question on most significant negative effect and a substantial proportion who did indicated cost or access issues, rather than physical or mental side effects. Though physical or mental side effects were probably minor or not present if the respondent indicated cost or access issues as the most significant negative effect, we don't know that for sure. We are unable to characterize most significant negative effect for those who did not submit a response.

Though the limitations mentioned in the paragraph above no doubt undercount the frequency of physical and mental side effects to some degree, their impact does not seem likely to

significantly change the main conclusions of the analyses reported in this section: at this point, the safety profile of the medical cannabis products available through the Minnesota program seems quite favorable.

Adverse Side Effects Reported on the Patient Self-Evaluation

Patients have the opportunity to report adverse side effects they attribute to medical cannabis on the Patient Self-Evaluation (PSE). Patients must complete a PSE prior to each medical cannabis purchasing transaction. Therefore, the administration of the PSE is timed so that patients can reflect on their experience with the medication they purchased previously and report those experiences on the following patient self-evaluation. A pharmacist at one of the eight medical cannabis dispensaries can then review PSE-reported information, which includes an opportunity to discuss side effects with the patient prior to approving that patient for another medical cannabis purchase. When reporting side effects on the PSE, patients are able to choose side effects from a pre-made list of options or write in side effects that do not fit one of the listed options. In addition, patients also indicate the severity with which each side effect is experienced (see Box 7.1).

Box 7.1. Definitions on severity provided to patients for adverse side effect reporting.

Adverse side effects were examined within the 1st program year cohort (n = 1660). Patients who had made at least their first medical cannabis purchase were identified, and from these patients, all PSEs that were

Adverse Side Effect Severity: Definitions

Mild: Symptoms do not interfere with daily activities

Moderate: Symptoms may interfere with daily activities

Severe: Symptoms interrupt usual daily activities

submitted within the four months following their first medical cannabis purchase were included in a dataset. This led to a total of 1502 patients (90.5% of the cohort) being represented. For the following analyses, each side effect was counted once for a given patient if it was reported multiple times. If a side effect was reported multiple times, the observation that was categorized at the highest severity level was included in the analyses for this report. In cases where a patient opted to write in their side effects (rather than choosing from the pre-made list of options), their responses were assessed carefully for adjudication for coding purposes. Therefore – while not affecting a substantial number of side effect responses – it should be noted that one limitation for accurate coding is the patient’s ability to adequately articulate their experiences.

Of the 1502 patients, 18.1% (n = 272) reported any adverse side effects within the four month period following their first medical cannabis purchase. Of those 272 patients reporting any adverse side effects, the majority reported only one (n = 164, 60.3%), with approximately 90% of them reporting three or fewer different, adverse side effects (Figure 7.1).

Figure 7.1. Distribution of patient counts by number of different, adverse side effects reported (out of 272 patients).

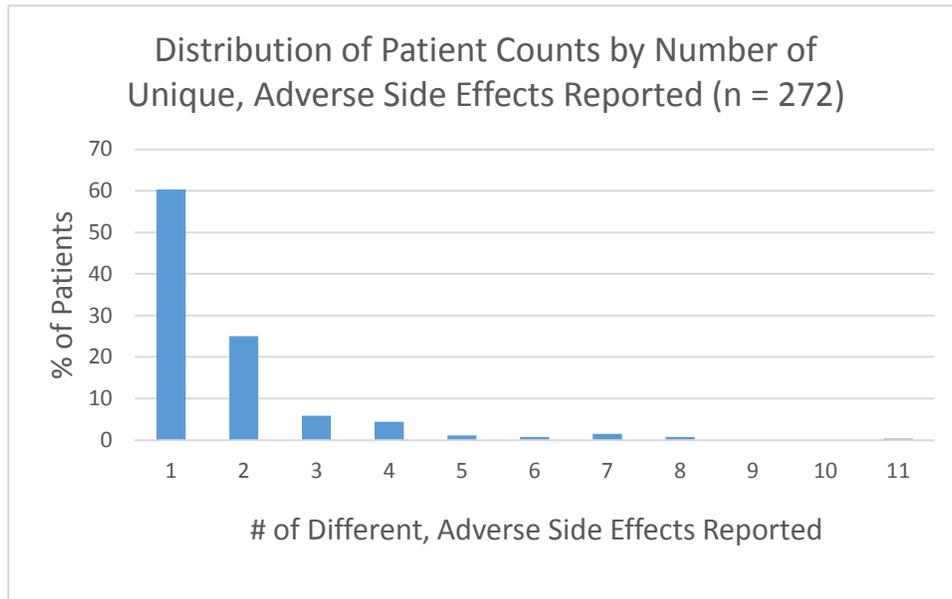


Figure 7.2 shows the percentage of patients reporting specific adverse side effects (Table 7.1 below lists adverse side effects that were reported by less than 2% of all patients). Of all side effects reported, dry mouth and drowsiness/somnolence/sedation were the most commonly reported side effects among patients. Overall, the frequency distribution of unique side effects mirrors typical clinical trial data on side effects from cannabis/cannabinoid use (see [“A Review of Medical Cannabis Studies relating to Chemical Compositions and Dosages for Qualifying Medical Conditions”](#) on the [Office of Medical Cannabis](#) website).

Figure 7.2. The most commonly reported adverse side effects represented by the percentage of patients reporting them (out of 272 patients).

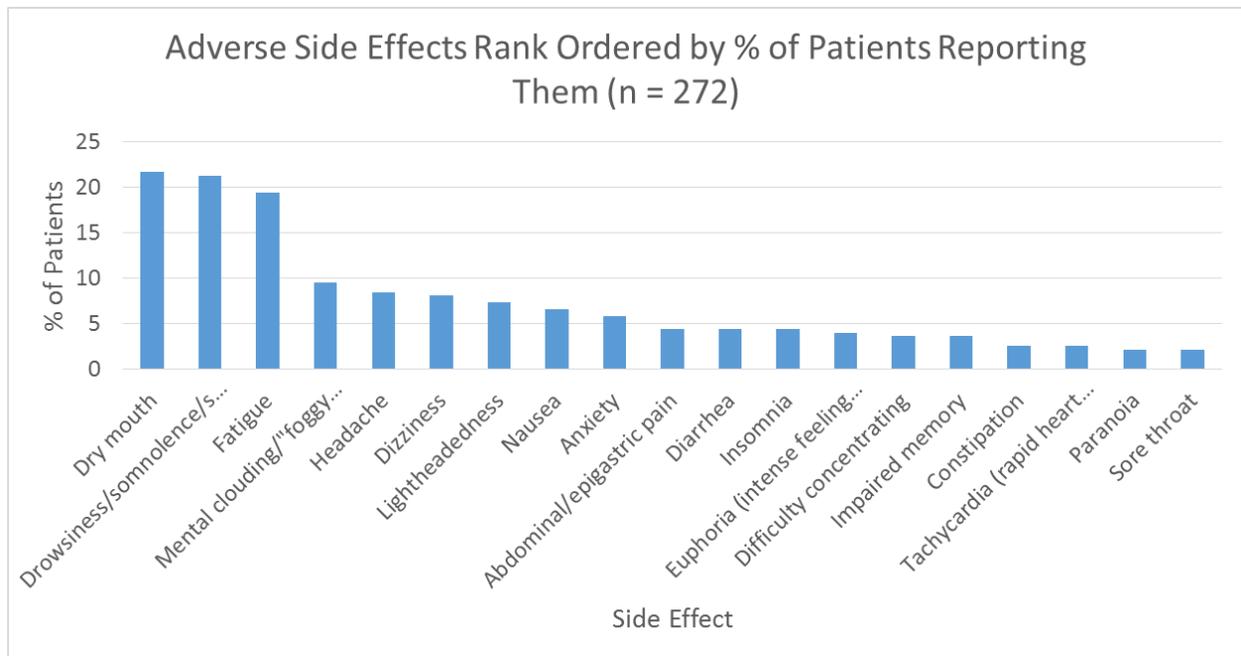


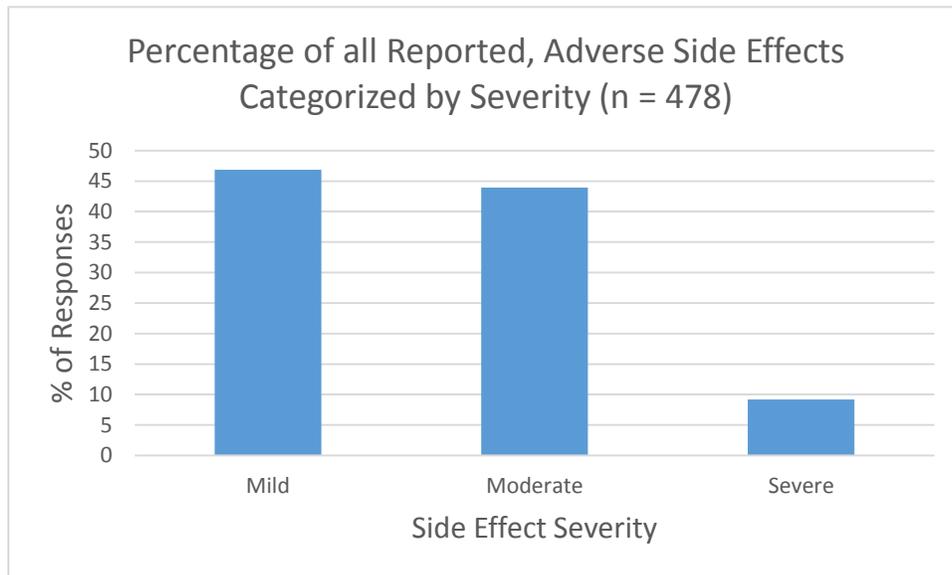
Table 7.1. Adverse side effects that were reported by less than 2% of patients (out of 272 patients).

Side Effect	% of Patients (n)
Asthenia (muscle weakness)	1.8% (5)
Chest pain	1.8% (5)
Confusion	1.8% (5)
Disorientation	1.5% (4)
Eye redness	1.5% (4)
Lethargy	1.5% (4)
Blurred Vision	1.1% (3)
Decreased muscle coordination/balance	1.1% (3)
Increased agitation	1.1% (3)
Numbness	1.1% (3)
Panic attack	1.1% (3)
Personality/mood change	1.1% (3)
Tinnitus (ringing perception in the ears)	1.1% (3)
"Stoned" feeling	0.7% (2)
Body stiffness	0.7% (2)
Coughing/lung irritation	0.7% (2)
Decreased appetite	0.7% (2)
Dry eyes	0.7% (2)
Feeling cold	0.7% (2)
Increased seizures	0.7% (2)
Tremors	0.7% (2)
"Wired" feeling	0.4% (1)
Bloating	0.4% (1)
Burping	0.4% (1)

Side Effect	% of Patients (n)
Change in quality of seizures	0.4% (1)
Chest colds	0.4% (1)
Cognitive change	0.4% (1)
Cramping with bowel movement	0.4% (1)
Dysphoria (intense feeling of unease or unpleasantness)	0.4% (1)
Exacerbation of lymphedema	0.4% (1)
Eye muscle twitching	0.4% (1)
Hives	0.4% (1)
Hyperactive bowel sounds	0.4% (1)
Hypomania	0.4% (1)
Increase in mucus secretions	0.4% (1)
Increased aggression	0.4% (1)
Increased urine output	0.4% (1)
Increased yelling	0.4% (1)
Mouth irritation/burning	0.4% (1)
Rash on face	0.4% (1)
Repressed immune system	0.4% (1)
Sleep disturbance	0.4% (1)
Sneezing	0.4% (1)
Thrush	0.4% (1)
Urinary retention	0.4% (1)
Vomiting	0.4% (1)
Worsening acne	0.4% (1)

The 272 patients reporting any adverse side effects submitted a combined total of 478 side effect responses within 4 months of their first medical cannabis purchase. When aggregating all side effect responses across patients, only 9.2% (44) of all responses were reported as severe (see Figure 7.3).

Figure 7.3. Percentage of all reported, adverse side effect responses categorized by severity.



Severe Adverse Side Effects

All adverse side effect responses that were categorized as severe are further broken down by the percent of patients categorizing them as such—please see Table 7.2 below.

Table 7.2. Table shows the number of patients reporting the listed side effects along with the percentage of those respondents who indicated that the side effect was severe.

Side Effect	# of Patients Reporting	% of Patients Reporting as Severe (n)
Dry mouth	59	6.8% (4)
Drowsiness/somnolence/sedation	58	5.2% (3)
Fatigue	53	3.8% (2)
Mental clouding/"foggy brain"	26	7.7% (2)
Headache	23	4.3% (1)
Dizziness	22	9.1% (2)
Lightheadedness	20	0% (0)
Nausea	18	11.1% (2)
Anxiety	16	12.5% (2)
Abdominal/epigastric pain	12	8.3% (1)
Diarrhea	12	16.7% (2)
Insomnia	12	8.3% (1)
Euphoria (intense feeling of well-being or pleasure)	11	9.1% (1)
Difficulty concentrating	10	20% (2)
Impaired memory	10	10% (1)
Constipation	7	14.3% (1)
Tachycardia (rapid heart rate)	7	28.6% (2)
Paranoia	6	16.7% (1)
Sore throat	6	0% (0)
Asthenia (muscle weakness)	5	60% (3)
Chest pain	5	20% (1)
Confusion	5	0% (0)
Disorientation	4	0% (0)
Eye redness	4	0% (0)
Lethargy	4	50% (2)
Blurred Vision	3	0% (0)
Decreased muscle coordination/balance	3	33.3% (1)
Increased agitation	3	0% (0)
Numbness	3	33.3% (1)
Panic attack	3	33.3% (1)
Personality/mood change	3	0% (0)
Tinnitus (ringing perception in the ears)	3	0% (0)
"Stoned" feeling	2	50% (1)
Body stiffness	2	0% (0)

Table 7.2 Continued. Table shows the number of patients reporting the listed side effects along with the percentage of those respondents who indicated that the side effect was severe.

Side Effect	# of Patients Reporting	% of Patients Reporting as Severe (n)
Coughing/lung irritation	2	0% (0)
Decreased appetite	2	0% (0)
Dry eyes	2	0% (0)
Feeling cold	2	0% (0)
Increased seizures	2	50% (1)
Tremors	2	0% (0)
"Wired" feeling	1	0% (0)
Bloating	1	0% (0)
Burping	1	0% (0)
Change in quality of seizures	1	0% (0)
Chest colds	1	0% (0)
Cognitive change	1	0% (0)
Cramping with bowel movement	1	0% (0)
Dysphoria (intense feeling of unease or unpleasantness)	1	0% (0)
Exacerbation of lymphedema	1	10% (1)
Eye muscle twitching	1	0% (0)
Hives	1	0% (0)
Hyperactive bowel sounds	1	0% (0)
Hypomania	1	0% (0)
Increase in mucus secretions	1	100% (1)
Increased aggression	1	100% (1)
Increased urine output	1	0% (0)
Increased yelling	1	0% (0)
Mouth irritation/burning	1	0% (0)
Rash on face	1	0% (0)
Repressed immune system	1	0% (0)
Sleep disturbance	1	0% (0)
Sneezing	1	0% (0)
Thrush	1	0% (0)
Urinary retention	1	0% (0)
Vomiting	1	0% (0)
Worsening acne	1	0% (0)

The 44 severe side effect responses (9.2% of total side effect responses) were attributed to 30 patients (11.0% of patients reporting any side effects). Patients experiencing severe side effects represent a wide range of ages, including children and elderly patients; 14 patients were male and 16 patients were female. Their age, gender, and certifying conditions generally matched the whole first year cohort. Half of patients reporting severe side effects were taking a form of balanced THC:CBD product (n=15); 10 patients were using a high CBD product, 9 patients were using a very high THC product and 4 patients were using a high THC product. Seven of 30 patients (23%) were using a combination of products with varying THC:CBD ratios (the most common combination was very high THC products and 1:1 THC:CBD products); 9 patients used a combination of products with different routes of administration (the most common combination was enteral and inhaled). Refer to Table 7.3 for details on the patients reporting severe side effects, along with the product types that were purchased just prior to experiencing the severe side effect.

PSE-Reported Adverse Side Effects: Conclusions

Less than a quarter of patients from the cohort (~18%) reported adverse side effects within the first 4 months since purchasing their first medical cannabis products. Roughly 90% of those that do report any side effects report 3 or fewer unique side effects during that time period. Results also suggest that relatively few patients experience severe, adverse side effects, with less than 10% of all responses (attributed to 30 patients) being categorized as severe.

Table 7.3. Patients reporting “severe” side effects: patient age, gender, and condition, product types purchased at most recent visit, and type of side effect reported.

Age	Gender	Condition(s)	Very High THC Product(s)	High THC Product(s)	High CBD Product(s)	1:1 THC:CBD Product(s)	Severe Side Effect Reported
55	M	HIV/AIDS	-	-	-	Enteral	Chest pain
67	F	Severe Muscle Spasms	Inhaled	-	Enteral	Enteral, Inhaled	Dry mouth
28	F	Severe Muscle Spasms	-	-	-	Enteral, Inhaled	Lethargy
58	F	Severe Muscle Spasms	-	-	-	Enteral, Inhaled	Panic attack
32	M	Severe Muscle Spasms	Inhaled	-	-	Inhaled	Asthenia (muscle weakness) Lethargy Tachycardia (rapid heart rate)
32	M	Severe Muscle Spasms	Inhaled	-	-	Inhaled	"Stoned" feeling
38	M	Severe Muscle Spasms	Inhaled	-	-	Inhaled	Insomnia
52	F	Severe Muscle Spasms	-	-	-	Enteral, Inhaled	Asthenia (muscle weakness) Drowsiness/somnolence/sedation
61	F	Cancer	-	-	Enteral	Enteral	Dry mouth
36	M	Seizures	-	-	Enteral	-	Diarrhea
41	M	Cancer, Terminal Illness	-	Enteral, Inhaled	-	-	Drowsiness/somnolence/sedation
87	F	Severe Muscle Spasms	-	Enteral, Oromucosal	-	-	Diarrhea
31	M	Cancer	Enteral, Inhaled	-	-	-	Nausea
71	F	Cancer	Inhaled	-	-	Enteral	

MINNESOTA MEDICAL CANNABIS PROGRAM: PATIENT EXPERIENCES FROM THE FIRST PROGRAM YEAR

							Asthenia (muscle weakness) Exacerbation of lymphedema
26	F	Terminal Illness	Inhaled	-	-	Enteral, Inhaled, Oromucosal	Constipation Difficulty concentrating Drowsiness/somnolence/sedation Dry mouth Mental clouding/"foggy brain"
36	F	Cancer	-	-	-	Enteral	Headache
33	M	Crohn's Disease	-	-	-	Enteral	Fatigue
63	F	Crohn's Disease	-	-	-	Enteral	Dizziness
82	M	Cancer	-	-	-	Enteral	Dizziness
60	F	Seizures	-	-	Enteral	-	Anxiety
32	M	Seizures	-	-	Enteral	-	Nausea
48	M	Seizures	-	-	Enteral	-	Fatigue
18	F	Seizures	-	-	Enteral	-	Increased seizures
28	M	Seizures	-	-	Enteral	-	Anxiety Paranoia
5	M	Severe Muscle Spasms, Seizures	-	-	Enteral	-	Decreased muscle coordination/balance Increased aggression
10	F	Seizures	-	-	Oromucosal	-	Abdominal/epigastric pain Increase in mucus secretions
56	F	Cancer, HIV/AIDS	-	Enteral	-	-	Dry mouth Euphoria (intense feeling of well-being/pleasure)
21	M	Cancer	-	Inhaled	-	-	Tachycardia (rapid heart rate)
42	F	Severe Muscle Spasms	Inhaled	-	-	-	

MINNESOTA MEDICAL CANNABIS PROGRAM: PATIENT EXPERIENCES FROM THE FIRST PROGRAM YEAR

							Impaired memory Difficulty concentration Mental clouding/"foggy brain"
45	F	Severe Muscle Spasms	Inhaled	-	-	-	Numbness

Adverse Side Effects Reported on Surveys

Patient-Reported Negative Effects of Medical Cannabis

For overall patient response rate to the survey three months after first purchase and comparison of responders and non-responders see the section with survey results in the Benefits chapter above.

The Patient Experience survey asks respondents to report the degree, or severity, of any negative effects they believe the patient received from using medical cannabis, on a scale from 1 (no negative effects) to 7 (a great deal of negative effects). The survey then asked the respondent to describe, in their own words, the most significant negative effect. Table 7.4 shows the distribution of negative effects by severity score within three broad categories: physical side effects (including dry mouth, fatigue, headache, dizziness, blurred vision); mental side effects (including mental clouding, paranoia, sedation or symptoms related to “high”); and issues related to accessing the medications (distance to distribution center, inconvenient operating hours for distribution centers, etc.). Based on anticipated reports on the high cost of medication, patients were asked to report on the affordability of the medication separately. However, 53 (7%) patients included cost in their estimation of the most significant negative effects related to medical cannabis; these reports are excluded from Table 7.4 but included in *Appendix E: Patient-Reported Negative Effects from Surveys*. Finally, please see the chapter titled, “Affordability and Suggestions for Improvement” for patient perceptions of medication affordability.

Of 792 completed patient surveys, 744 responses (94%) included a negative effects score and 441 (56%) included a response regarding most important negative effect, including comments stating “no negative effect.” Of 744 negative effect scale responses, 452 (61%) reported a score of 1, or “no negative effect.” This includes 13 patients who, though they entered a score of 1, entered a narrative description of physical or mental side effects. A total of 195 responses (25% of all patient responses) reported physical or mental negative effects. These reports generally mirrored side effects reported in clinical trials of medical cannabis (see “[A Review of Medical Cannabis Studies relating to Chemical Compositions and Dosages for Qualifying Medical Conditions](#)” on the [Office of Medical Cannabis](#) website). Reports of the most severe negative effects were as follows: scores of 7 (great deal of negative effects) were associated with reports of allergic reaction (n=1), pain (n=1), severe diarrhea (n=1), change in mood/behavior (n=1) and decreased awareness of surroundings (n=1). Scores of 6 were associated with reported physical side effects of dizziness or related symptoms (n=3), severe diarrhea (n=1), stomach pain (n=1), burning sensation with sublingual product (n=1), sleeping problems (n=1) and worsening seizures (n=2), and mental side effects of crying and irritability (n=1). Scores of 5 which reported physical negative effects included drug interactions, increased seizure activity, allergic reaction, lightheadedness, fatigue, headaches, visual impairment, dry mouth, a report that the

product “made me sick” and pain related to vaping (n=1 each). Scores of 5 which reported mental negative effects included reports of paranoia (n=2), inability to concentrate (n=1), and increased anxiety (n=1).

Apart from physical or mental negative effects, some patients reported issues related to program access, including distance to the nearest cannabis patient center (n=13). Other negative effects (not included in Table 7.4) were reported including issues related to the program design (n=9), negative attitudes of others toward the patient’s use of medical cannabis (n=17) and fear of legal or employment-related consequences related to program participation (n=5). Finally, 16 reports of negative effects were related to lack of efficacy of the medicine in treating the patient’s condition. A full listing of patient-reported negative effect comments is available in *Appendix E: Patient-Reported Negative Effects from Surveys*.

Table 7.4. Summary of most significant negative effects experienced by the patient, per patient reports.

	1: No Negative Effects	2	3	4	5	6	7: Great Deal of Negative Effects	Total
Physical Side Effects	10 (1%)	57 (7%)	15 (2%)	26 (3%)	10 (1%)	9 (1%)	3 (0%)	130 (16%)
Mental Side Effects	3 (0%)	18 (2%)	14 (2%)	19 (2%)	4 (1%)	1 (0%)	2 (0%)	61 (8%)
Access-Related Issues	4 (1%)	3 (1%)	1 (0%)	2 (0%)	1 (0%)	1 (0%)	1 (0%)	13 (2%)

Note: Results are broken down by negative effect scale scores. Percentages are calculated based on the total number of patient survey responses received (n=792).

HCP-Reported Negative Effects from Medical Cannabis

Like the Patient Experience survey, the HCP survey asks respondents to report the degree, or severity, of any negative effects they believe the patient received from using medical cannabis, on a scale from 1 (no negative effects) to 7 (a great deal of negative effects). Table 7.5 shows the distribution of negative effects by severity score within three broad categories: physical side effects (including dry mouth, fatigue, headache, dizziness, blurred vision); mental side effects (including mental clouding, paranoia, sedation or symptoms related to “high”); and issues related to accessing the medications (long distance to distribution center, inconvenient operating hours for distribution centers, etc.).

Of 251 total HCP survey responses, 200 responses (80%) included a negative effects score and 107 responses (43%) included a description of any negative effect(s). Of 200 negative effect scale responses, 128 (64%) reported a score of 1, or “no negative effect.” This includes 6 HCP

reports which entered a narrative description of physical or mental side effects. There were 33 HCP reports (13% of all HCP survey responses) of physical or mental negative effects resulting from medical cannabis treatment. As seen in the patient survey results, these generally mirrored side effects described in clinical trials (see [“A Review of Medical Cannabis Studies relating to Chemical Compositions and Dosages for Qualifying Medical Conditions”](#) on the [Office of Medical Cannabis](#) website). Healthcare providers describing negative effects with high scores reported the following: a score of 7 was associated with a report of “abdominal discomfort”; dizziness (n=1) and sedation (n=1) were reported with scores of 6; finally, constipation, lethargy and worsened seizure activity (n=1) and a report of “too strong per patient” (n=1) were associated with a score of 5. Four HCP responses reported access-related issues as a negative effect. Additionally, 25 HCP reports (10% of all HCP survey responses) described cost as a negative effect related to medical cannabis (these reports are not included in Table 7.5).

A full listing of all negative effect comments from HCPs can be found in *Appendix F: Healthcare Practitioner-Reported Negative Effects from Surveys*.

Table 7.5. Summary of most significant negative effects experienced by the patient, per HCP reports.

Negative Effects By Score (1-7 Scale)	1 (No Negative Effects)	2	3	4	5	6	7 (Great Deal of Negative Effects)	Total
<i>Physical Side Effects</i>	4 (2%)	5 (2%)	6 (2%)	2 (1%)	1 (0%)	1 (0%)	1 (0%)	20 (8%)
<i>Mental Side Effects</i>	2 (1%)	6 (2%)	3 (1%)	1 (0%)	-	1 (0%)	-	13 (5%)
<i>Access Issues</i>	1 (0%)	2 (1%)	1 (0%)	-	-	-	-	4 (2%)

Note: Results are broken down by negative effect scale scores. Percentages in each cell are based on the total number of HCP survey responses (n=251).

Adverse Side Effects Reported on Surveys: Conclusions

Based on data from surveys completed by patients and their certifying healthcare practitioners three months after the patient’s first medical cannabis purchase, 25% of patient respondents report physical or mental side effects related to medical cannabis use. A minority of healthcare provider responders (13%) report physical or mental side effects. Both groups describe negative effects related to medical cannabis use including the cost of products and issues related to

accessing medicine. Most patients and HCPs reporting physical or mental side effects report low degrees of severity (negative effect scale scores of 1-3).

Adverse Event Reporting to Manufacturers

There is potential for enrolled patients, their family and caregivers, and health care practitioners to be concerned about an adverse event potentially caused by medical cannabis and to want to register their concern quickly. Both manufacturers have processes in place to receive these messages by telephone and by email. They collect and document information related to the incident and report it to the Office of Medical Cannabis. In nature and severity these reports have been similar to the adverse events reported in Patient Self-Evaluations and surveys.

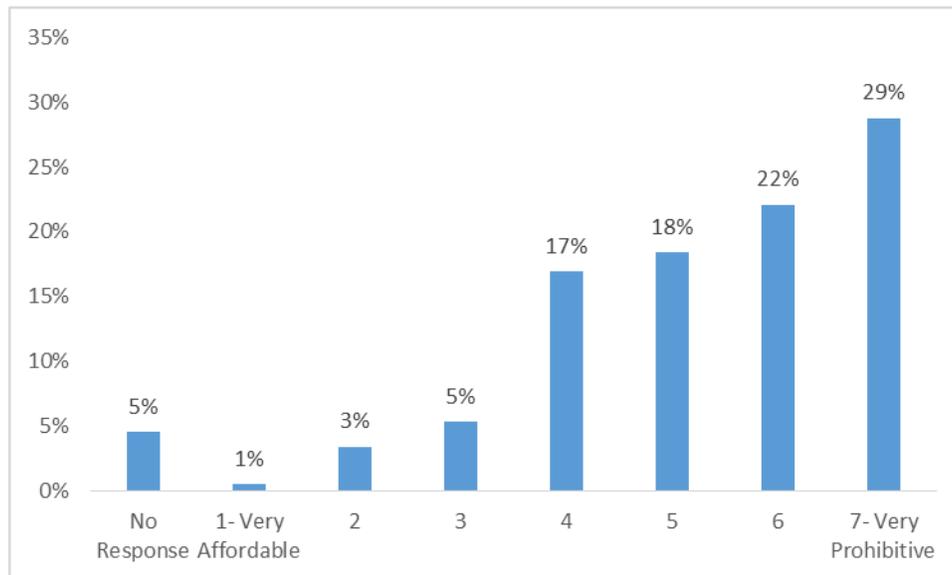
Patients, their registered caregivers, and certifying health care practitioners have a duty as program participants to report serious adverse events. Called “serious adverse incidents” in the program’s rules (4770.4002), these are essentially occurrences that lead to hospitalization or are life-threatening events. As of the date of this report, no reported adverse events have met the definition of “serious adverse incident.”

8. Affordability and Suggestions for Improving the Program

Patient Perceptions of Affordability

Unlike traditional pharmaceuticals whose costs are often covered through insurance reimbursement, medical cannabis must be purchased solely out of pocket. The Patient Experience survey asked patients to rate the cost of the medication on a scale from 1, or very affordable, to 7, or very prohibitive. Responses to this question are displayed in Figure 8.1. Of 792 respondents, 683 (86%) reported that they found medical cannabis to be at least somewhat unaffordable (score of 4 or greater).

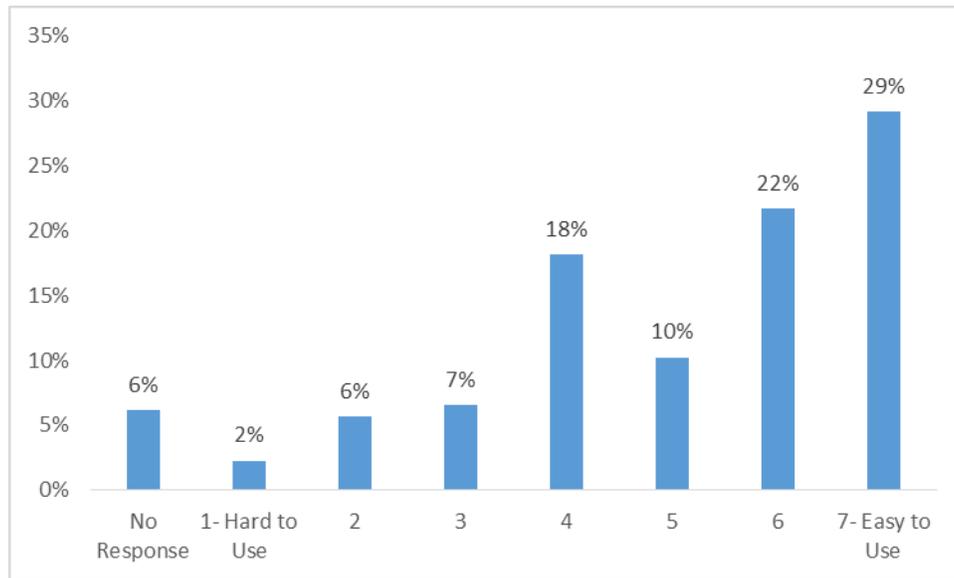
Figure 8.1. Patient Perceptions of Product Affordability



Patient Perceptions of Online Registry

Patients were asked how easy or difficult the online registry system, through which the Minnesota Medical Cannabis program is administered, is to use. Patients were asked to rate usability on a scale from 1, or very difficult to use, to 7, or very easy or intuitive to use. Responses were generally positive (Figure 2), with 51% of patients reporting high scores of usability (6 or 7).

Figure 8.2. Online Registry Ease of Use

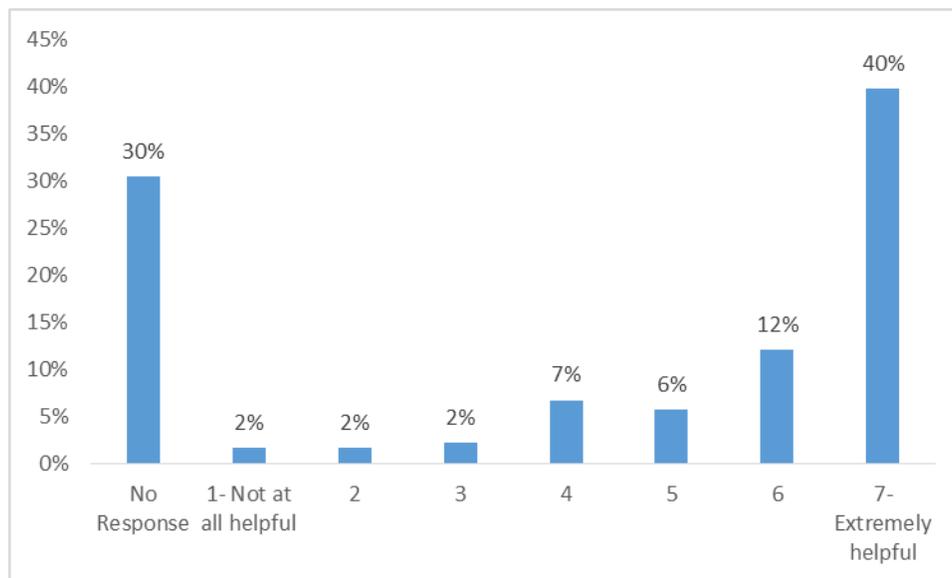


Patient reports on the ease of use of the Medical Cannabis Registry online system (1=very difficult to use; 4=neither difficult nor easy to use; 7=very easy/intuitive to use). Note: percentages are based on total number of patient responses; 49 patients did not complete this question and are not represented in the figure.

Patient Perceptions of Office of Medical Cannabis Call Center

Patients were asked to rate the helpfulness of the Office of Medical Cannabis Call Center (also known at the Support Center), which provides support for patients, caregivers and providers in navigating the registration and enrollment process as well as assisting with other program-related inquiries. The Patient Experience survey asked patients to rate the helpfulness of the call center on a scale from 1, or not very helpful, to 7, or very helpful. Over half of all patient responses reported high scores of helpfulness (6 or 7).

Figure 8.3. Call Center Helpfulness

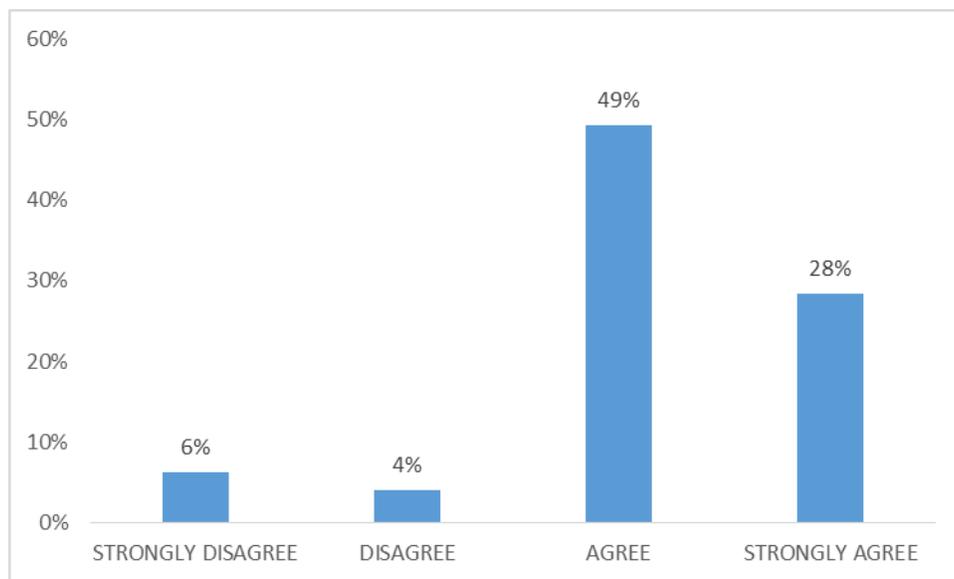


Patient reports on the helpfulness of the Office of Medical Cannabis Patient Support Center (1=not very helpful; 4=somewhat helpful; 7=very helpful). Note: percentages are based on total number of patient responses; 241 patients did not complete this question (several indicated no experience with the call center) and are not represented in the figure.

Patient Perceptions of Office of Medical Cannabis Website

Patients were asked to state their level of agreement with the statement: “The Office of Medical Cannabis website provides me with the information I need to understand and participate in the program.” Among all patient respondents, 49% agreed and 28% strongly agreed that the website met their needs for information; however 10% expressed that they did not feel the website met their needs for program participation (Figure 8.4) and 12% did not respond to the survey question.

Figure 8.4. “The website provides the information I need to understand and participate in the program”



Patient Suggestions

Patients were asked to provide feedback on the program; all responses submitted from the first year cohort are tabulated in *Appendix G: Patient Suggestions for Improving the Program from Surveys*. Many patients used this space to elaborate on the program’s impact on their lives; others suggested changes to the program’s administration or reported concerns related to product cost or access to cannabis patient centers.

Suggestions and Information Requests from Healthcare Practitioners

Healthcare practitioners were asked to provide suggestions for improving the program, and were also asked if any additional information from the program would be useful to them. The full tabulation of comments is available in *Appendix H: Healthcare Practitioner Suggestions for Improving the Program and Requests for Additional Information from Surveys*. Many comments reported in these sections of the survey mirrored those reported as clinical observations; there were 39 additional comments relating to affordability of the products. Other common responses included requests for information on medical cannabis dosing and specific information on what products their patient was purchasing. Other responses included requests for more patient education regarding products, information on drug interactions, and data on efficacy in specific patient populations.

REVIEW

Open Access



Sleep abnormalities associated with alcohol, cannabis, cocaine, and opiate use: a comprehensive review

Gustavo A. Angarita, Nazli Emadi, Sarah Hodges and Peter T. Morgan*

Abstract

Sleep abnormalities are associated with acute and chronic use of addictive substances. Although sleep complaints associated with use and abstinence from addictive substances are widely recognized, familiarity with the underlying sleep abnormalities is often lacking, despite evidence that these sleep abnormalities may be recalcitrant and impede good outcomes. Substantial research has now characterized the abnormalities associated with acute and chronic use of alcohol, cannabis, cocaine, and opiates. This review summarizes this research and discusses the clinical implications of sleep abnormalities in the treatment of substance use disorders.

Keywords: Sleep, Insomnia, Alcohol, Cannabis, Cocaine, Opiates

Background

Sleep problems are commonly associated with drug and alcohol use. Nearly 70 % of patients admitted for detoxification report sleep problems prior to admission, and 80 % of those who report sleep problems relate them to their substance use [169]. The association between substance use and sleep problems appears to be bidirectional [105, 110], with sleep problems increasing risk for developing substance use disorders [31, 89, 210], and acute and chronic substance use leading to acute and chronic problems with sleep [44, 47, 89, 97, 104, 138, 156, 168]. Evidence also indicates that long-term abstinence from chronic substance use can reverse some sleep problems [13, 37]. This paper aims to explore and clarify the strong yet not entirely understood connection between abnormalities in sleep and substance use. By improving our understanding of sleep disorders that either predispose to substance use or are the result of chronic substance use, we may be better able to prevent and treat substance use disorders.

Understanding the sleep problems related to substance use disorders requires characterizing them both

subjectively and objectively, while considering how sleep responds to periods of use and abstinence. This review will describe such research with regard to alcohol, cannabis, cocaine, and opioids. In addition, this review will discuss evidence that sleep abnormalities predict use and relapse, and that sleep abnormalities can be modulated to improve clinical outcome. This paper will also review potential pharmacological agents that modulate sleep. Psychotherapy options, albeit evidence-based and of clear clinical value, will not be discussed in this review as these are addressed elsewhere [15, 110].

Methods

This is a narrative, non-systematic review of clinical trials conducted in humans. For the literature search, Pubmed, Ovid Medline, and Web of Science databases were used. For each drug (e.g., alcohol, cannabis/marijuana, cocaine, and opioids/heroin) keywords included terms describing abnormal/pathological use (e.g., alcohol use disorders, alcohol abuse, alcohol dependence, and alcohol addiction, etc.) combined with terms referring to sleep or sleep abnormalities [e.g., sleep, insomnia, polysomnography, total sleep time, slow-wave sleep, rapid eye movement (REM) sleep, sleep latency, REM latency; these terms are defined in Table 1]. In addition to extracting data available in each of the retrieved articles, reference lists from

*Correspondence: peter.morgan@yale.edu
Yale University Department of Psychiatry, Connecticut Mental Health Center, 34 Park Street, New Haven, CT 06519, USA

Table 1 Sleep terminology

Homeostatic sleep drive	The drive to sleep that progressively builds with continued wakefulness
Insomnia	A sleep disorder in which the quantity or quality of sleep is less than desired, usually characterized by difficulty falling or staying asleep, or waking too early, and experiencing daytime consequences of reduced sleep
Polysomnography (PSG)	A technique that records brain activity, eye movements, and muscle tone in order to study sleep and diagnose sleep disorders
Rapid eye movement (REM) sleep	The phase of sleep characterized by conjugate eye movements, paralysis of other muscles, and brain activity that is most similar to wakefulness
REM density	The frequency of rapid eye movements occurring during REM sleep. REM density increases over the course of the sleep period and is greatest when homeostatic sleep drive (sleep pressure) is lowest
REM latency	The amount of time from the onset of sleep to the onset of REM sleep
REM rebound	The characteristic increase in REM sleep after REM sleep deprivation
Self-administration	A method involving research participants administering a substance to themselves under observation in a clinical setting
Sleep architecture	The structure of sleep, including non-REM (stages N1, N2, and N3) and REM (stage R) sleep
Sleep efficiency (SE)	The percent of time in bed spent sleeping, calculated as total sleep time divided by time in bed
Sleep fragmentation	Disruption in sleep characterized by awakenings and transitions to light (stage N1) sleep from deeper sleep
Sleep latency (SL)	The amount of time from lights out to sleep onset
Slow-wave sleep (SWS)	Also known as stage N3 sleep, slow wave sleep is characterized by low frequency and high amplitude waves
Total sleep time (TST)	The amount of sleep in one complete episode of sleeping, usually reported in minutes
Wake after sleep onset (WASO)	The amount of time awake after the onset of sleep and before final waking

each retrieved article were examined to identify articles missed by the initial search. For each drug, the available literature on subjective measurements, objective measurements, the relationship between subjective and objective measurements, clinical and laboratory correlates of sleep outcomes, and pharmacotherapies related to sleep were summarized.

Alcohol

Subjective measurements

Alcohol is widely used as a sleep-promoting agent. However, as the consumption of alcohol becomes chronic, alcohol has less of an hypnotic effect [196]. Significant, self-reported sleep problems are highly prevalent among alcohol users with rates of clinical insomnia between approximately 35 and 70 % depending on the setting and stage of use, among other parameters [35, 48]. These rates are substantially higher than those observed in the general population (i.e. ~15 to 30 %) [32]. Complaints typically include difficulty falling asleep, frequent awakenings, daytime sleepiness, and abnormal sleep quality [15, 34, 196], but could also include hypersomnia [196]. Notably, sleep complaints associated with alcohol use disorders are one of the most refractory problems to resolve [34, 69, 82], and insomnia is the most frequent complaint among alcoholics after they stop drinking [132].

Objective measurements

Objective measurement of sleep in persons with alcohol use disorders confirms self-reported sleep problems in

many respects, and provides additional insight into the nature of the underlying sleep abnormalities.

Sleep latency (SL)

Although it is known that alcohol can decrease sleep latency when consumed by healthy persons [124], chronic use leads to increased sleep latency, consistent with individual self-report. Published studies show that SL is prolonged during periods of drinking [9, 33, 85, 199, 221], during acute withdrawal (e.g., weeks 1 and 2 of abstinence) [9, 33, 85, 199, 221], and during post-acute withdrawal (e.g., weeks 2 through 8) [33], (Table 2) with evidence for sleep latency prolongation in inpatient and outpatient settings (e.g., [83, 123, 183]), and when controlled for age and sex, among other variables [26]. After the second month of abstinence, sleep latency may still be increased [213], or normalized [174], with evidence for normalization also present after five [69] and 9 months of abstinence [213].

Total sleep time (TST)

Congruent with increased sleep latency, total sleep time is reduced in persons with alcohol use disorders during periods of drinking, acute withdrawal, and post-acute withdrawal [33, 85, 86, 199, 221], with very few exceptions [9]. Numerous studies examining total sleep time from 2 to 4 weeks of abstinence document reduced sleep time compared to healthy controls [69, 83, 183] (Table 2). Reduced total sleep time has also been observed in study

Table 2 Objective sleep changes during early and late abstinence, in comparison to healthy sleepers

	Alcohol		Cocaine		Cannabis		Opioids	
	Early Abs	Late Abs						
Sleep latency	?	↑	?	↑	↑	?	↑	↑
Total sleep time	?	↓	?	↓	↓	↓	↓	↓
Slow wave sleep	?	↓	↓	↓	↓	?	↓	↓
REM sleep	?	?	?	↓	↑	↓	↓	?
REM latency	?	?	↓	?	↓	?	↑	?

Early Abs Early Abstinence or acute withdrawal

Late Abs Late Abstinence or subacute withdrawal

? Insufficient data or conflicting results across studies

designs that control for age and sex, among other variables [26].

Total sleep time in persons with alcohol use disorder may improve after sustained abstinence. For instance, one group found decreased yet gradually improving TST among alcoholic subjects after 19 weeks, 14, and 27 months of abstinence (312, 335, and 349 min, respectively) [69]. Another study examined TST after 1–2 years of abstinence and found no abnormalities among subjects recruited from Alcoholics Anonymous vis-à-vis controls [2].

Slow-wave sleep (SWS)

Considerable evidence points to deficits in slow wave sleep time (i.e. stage 3 and stage 4 sleep, or stage N3 sleep in the newer nomenclature) or slow-wave sleep activity (i.e. EEG spectral power in the slow wave frequency range) in persons with alcohol use disorders [33]. Most of this evidence comes from studies reporting results from the first few weeks of abstinence, including acute withdrawal [196], subacute withdrawal (i.e. days 8 and 12); [106] (Table 2), and beyond [26, 69, 83, 127].

Although there is evidence that SWS deficits are recovered with prolonged abstinence, current literature does not provide a definitive time frame for these improvements, yet does suggest that it may be between 3 and 14 months [33] or longer. While one study found no difference between alcohol users and controls at 25 days abstinent [183], other studies found that SWS had improved at 3 months, and normalized at 9 months of abstinence [196]. In contrast, other studies have reported persistent deficits [69] or a trend toward deficits [2] after as long as 1–2 years of abstinence, with complete recovery occurring only after 1–4 years of abstinence [199].

Intriguingly, acute alcohol use has been shown to reverse the chronic slow wave sleep deficits observed in chronic alcohol users [33, 86]. Given the widespread importance of slow-wave sleep [65] in factors including

sleep continuity, learning, and memory, as well as other types of cognitive performance, the deficits associated with chronic use (and their reversal with acute use of alcohol) suggests the particular importance of slow-wave sleep in alcohol use disorders. More specifically, as the brain processes that underlie the generation of these slow waves appear to be chronically altered by chronic alcohol use, and to be temporarily restored by acute use, this chronic alteration is implicated as a potential factor in relapse.

Rapid eye movement (REM)

For both persons without alcohol use disorders (AUD) [118, 219] and individuals with alcohol use disorders, drinking alcohol acutely suppresses REM sleep time. For persons with AUD, REM rebound occurs several days later [33]. An early study of sleep in persons with AUD who were exposed to alcohol found that REM sleep, measured as a percentage of total sleep time (REM%) was less, relative to baseline, after 2–3 days of abstinence, but then rebounded after 5–6 days of abstinence [7]. This rebound in REM sleep has been explained as reflecting both an increased number of REM periods as well as shorter intervals between each REM cycle [196]. REM rebound has been documented after 2–3 weeks of abstinence [26, 69, 83, 127], and even after 27 months of abstinence [69].

Notwithstanding the above findings, the literature on alcohol and REM sleep has some inconsistencies (Table 2). For example, a meta-analysis examined six studies that did not consider covariates and four studies that controlled for variables such as age and sex (all participants abstinent for at least 3 weeks). Even though the analyses among all subjects showed no differences in REM measured as the percentage of total sleep (REM%), the analyses did find increased REM% in persons with AUD compared to controls when controlling for some variables [26]. Other studies have found

no difference in REM% between chronic alcohol users and normal controls in the second [106] and third [83] week of abstinence. Additionally, supporting the finding of no difference in REM between chronic alcohol users and controls, a study examining REM time after 4 weeks of abstinence found no difference between subjects with AUD and normal controls [183]. Another discrepancy appears in the form of a study that found REM% among participants with AUD to be reduced after 12 weeks of abstinence in comparison with REM% after 4 weeks of abstinence, arguing against a lasting REM rebound [171].

Possibly contributing to differences in REM sleep findings are variations across studies in how control participants were recruited [183] and how well these control subjects matched the subjects with AUD in terms of measures relevant to sleep architecture such as age. An example of this is a meta-analysis exhibiting different results depending on whether authors controlled for those variables or not [26]. Another factor could be that several studies report REM%, thus, the numbers are also a reflection of not one, but two sleep architecture measurements (e.g., REM and TST) that are both undergoing dynamic changes as subjects with AUD progress in abstinence [69].

REM latency

Data on REM latency in persons with alcohol use disorders is more limited but also show some discrepancies. For instance, while some studies report that REM latency is decreased during the second week of abstinence [69, 106], as well as up to two years later [69], other studies do not report differences in REM latency [26, 32] (Table 2). One potential explanation for the inconsistencies in this measure could lie in the heterogeneity of subjects with AUD with regard to co-occurring conditions like depression. Supporting this idea is the finding that AUD subjects with secondary depression exhibit shorter REM latency compared to AUD subjects who do not have secondary depression [83].

Objective sleep quality or consolidation of sleep

Several studies examining sleep in persons with alcohol use disorders also reported data on fragmentation of sleep. Sleep fragmentation reflects awakenings or switching from a deeper to a lighter stage of sleep, and is measured by the number of switches from one stage of sleep to another, the number of awakenings, and the time spent awake after sleep onset. The measurements of sleep fragmentation provide some insight into the objective quality of sleep. Results from these studies show consistent deficiencies in objective sleep quality, with an increase in sleep stage switches compared to healthy controls from day 2 of abstinence to as far out as 1–2 years of abstinence [2, 106, 196].

Sleep stage switches, number of awakenings and time awake after sleep onset were also found to be increased on the second night of abstinence compared to the second week of abstinence, which suggests greater abnormalities in objective sleep quality occur during the withdrawal period [106]. In addition, increased sleep fragmentation was observed after 3 and 9 months of abstinence [196].

Relationship between subjective and objective outcomes

Although there is limited published data on the relationship between subjective and objective sleep measurement in persons with alcohol use disorders, one group studied 172 individuals with alcohol use disorders of whom 104 had insomnia as determined by the Sleep Disorders Questionnaire [35]. They found that participants with baseline insomnia had longer sleep latency and lower sleep efficiency at an average of approximately 1 month abstinent than those without, suggesting a correspondence between self-report and objective measurement.

Clinical and laboratory correlates of subjective and objective sleep outcomes

In a small study, increased sleep latency associated with chronic alcohol use was linked with lower overall melatonin levels as well as with a delay in the onset and peak of melatonin [123]. A much larger study found an association between increased sleep latency and decreased sleep efficiency among persons with AUD and sleep disorder breathing [6].

In patients with AUD, insomnia is also correlated with amount of alcohol use [22], severity of alcohol use disorder [35], and self-report of alcohol use as a sleep aid [35]. An association between insomnia and severity of self-reported depression symptoms has also been recognized [35].

Relationship between subjective measurements and clinical outcomes

Several studies among alcohol AUD subjects have documented the relationship between self-reported insomnia and clinical outcomes. These studies examined the effects of 1 week of abstinence while undergoing inpatient admission (e.g., subjects who self-reported insomnia during this week had higher likelihood of choosing to drink as part of a subsequent inpatient period in which this option was allowed) [182], and showed similar results after following subjects for 3 months post-detoxification (e.g., compared to subjects who did not relapse during this period, subjects who did relapse were more likely to answer “yes” to the statement, “It takes me a long time to fall asleep” from the Nottingham Health Profile [NHP] or, “I sleep badly at night,” as part of their baseline assessments) [76], or after

following subjects for 5 months (e.g., having insomnia based on the Sleep Disorders Questionnaire after 2 weeks of abstinence was a predictor of relapse). Also, subjects who relapsed after 5 months had more baseline complaints of difficulties falling asleep and abnormal sleep than the group who did not relapse [34, 35].

Relationship between objective measurements and clinical outcomes

Mixed findings implicate objective sleep measurements as predictors of clinical outcomes in AUD. For example, increased sleep latency measured within the first 2 weeks of inpatient admission increased the odds of relapse to alcohol use within the following 5 months [34]. Similarly, increased sleep latency and decreased sleep efficiency after 16 days and 19 weeks of abstinence were associated with lower rates of abstinence at 14 months [69]. However, one study found no difference in sleep latency at 5 days abstinent between persons who subsequently relapsed and those who remained abstinent [82].

Two studies have reported a connection between slow-wave sleep and clinical measures in persons with AUD. Slow-wave sleep time was inversely correlated to the maximum number of withdrawal symptoms reported during subacute withdrawal (8–32 days of abstinence) [83], and lower percent of stage 4 NREM sleep was associated with relapse [34]. However, another study found no difference in slow-wave sleep between relapsers and abstainers [82].

Similar to clinical studies examining sleep latency and SWS, REM sleep measurements appear to be important in clinical outcomes, but with conflicting results. The differences observed here might be consistent with the differences in the measurement of REM sleep in persons with AUD described above. For instance, while one study indicated a positive correlation between low REM% with response rate in a button-press task to obtain an alcoholic drink [8], Gillin et al. showed increased REM% and shorter REM latency upon admission and upon discharge from a four-week admission among relapsers in comparison with abstainers [82]. Another study showed that increased REM latency decreased the odds of relapsing [34], and one study found no connection between REM latency measured at 19 weeks of abstinence and subsequent relapse [69]. The variation in results regarding REM sleep may be due to the different effect that acute and chronic use, have on REM sleep, and be due to changes in REM sleep as the number of days abstinent increases. Another important consideration is that achieving long periods of abstinence (e.g., like 19 weeks) is in general a good predictor of abstinence and does so to a much greater degree than the predictive qualities of other physiological measurements obtained early in abstinence.

Pharmacotherapy options targeting sleep abnormalities

Because of the profound effects of chronic alcohol use and sleep and the apparent connection between sleep measures and clinical outcome, several studies have examined the role of sleep-promoting medications in treating persons with AUD (for review see [119]). In double-blind, placebo-controlled and other trials, gabapentin has been studied with largely [112, 136, 137] but not entirely [39] positive results. These studies suggest that gabapentin may promote both sleep outcomes and abstinence [137] in persons with alcohol use disorders.

Given the suggestion that melatonin levels are decreased in alcoholics [177, 212], the melatonin receptor agonists ramelteon and agomelatine have been examined in case series. Among patients who had been abstinent for 2–13 weeks, ramelteon was associated with decreased scores on the Insomnia Severity Index (ISI), decreased sleep latency, and increased total sleep time measured by actigraphy [36]. Similarly, agomelatine was associated with improved sleep as measured by the Pittsburgh Sleep Quality Index after 6 weeks [87].

Another potential pharmacotherapeutic agent that has been studied in this population is quetiapine. In a double-blind, placebo-controlled trial, quetiapine was associated with improvements in time awake after sleep onset and subjective insomnia [53]. In addition, a retrospective study showed an improvement on the insomnia subscale of the HAM-D [173] with quetiapine. The effect of quetiapine on alcohol-related clinical outcomes has been mixed, with evidence for improvement in abstinence rates in one study [142], and increased risk of re-hospitalization in another [143].

Trazodone is widely prescribed as a sleep aid in persons with addictions because of its lack of addictive potential. Although studies of trazodone in persons with AUD has shown benefits in sleep measurements [125] in a large, placebo-controlled trial, those benefits on sleep quality did not result in clinical improvement, but rather trazodone was associated with less abstinence during treatment and an increase in drinking after cessation of treatment [79]. Findings like these suggest that the relationship between sleep physiology and alcohol use and relapse is not simple. Rather, treatments directed at sleep that improve qualitative sleep but do not address the underlying physiological changes associated with chronic alcohol use may not be expected to promote abstinence.

Unlike trazodone, the popular benzodiazepine and benzodiazepine-like agents are often avoided in persons with alcohol use disorders because of their addictive potential and the increased risk of toxicity or overdose when these medications are mixed with alcohol [16, 90].

Cannabis

Subjective measurements

Like alcohol, cannabis may improve subjective sleep complaints [56], particularly when used over short periods of time. For instance; in studies using self-report questionnaires (e.g., Leeds Sleep Evaluation Questionnaire) participants report greater ease in getting to sleep [50]. However, like alcohol, chronic cannabis use is associated with negative subjective effects on sleep that are manifested most prominently during withdrawal. Notably, these subjective effects are present during discontinuation of cannabis use even among persons who were exposed to low dosages [97], and are common among regular users [61, 188]. Symptoms reported include sleep difficulties [61] such as strange dreams, insomnia, and poor sleep quality. Such symptoms occur in anywhere from 32 % [58] to 76 % [27, 222] of persons experiencing withdrawal. These studies have been conducted in both the inpatient (residential) [61, 97, 98] and outpatient levels of care [42, 44], and in studies with as many as 450 participants [222]. Placebo-controlled studies have examined what happens after discontinuation of oral THC use [97] or after discontinuation of smoked marijuana [98]. Regardless of design, studies of the effects of chronic use have consistently shown reliable and significant changes in subjective reports of sleep during abstinence in comparison to baseline [42].

Among the problems with sleep in chronic cannabis users is the presence of strange dreams [44]. Such dreams typically begin 1–3 days after cannabis discontinuation—when sleep quality is particularly poor [42, 44, 195], peak after 2–6 days, and last 4–14 days [44], coincident with other subjective sleep complaints. However, large studies have found sleep difficulties lasting for longer periods, such 43 days [58], and strange dreams in particular lasting for as long as 45 days [44]. Returning to cannabis use (or using alcohol or other sedatives) to promote sleep is commonly observed [58].

However, the sleep-promoting effect of cannabis is lessened in the chronic user compared to naïve users [50–52, 91], while the negative effects of cannabis on sleep intensify with chronic use as noted above. This scenario leaves the chronic user in a potential catch-22: heavier use of cannabis may be necessary to receive its subjective sleep-promoting effects in the chronic user, but at the same time this increased use contributes to worsening overall sleep and therefore leads to continued and greater use.

Objective measurements

Studies examining the effect of cannabis on objective sleep measurements obtained either by an experienced observer rating sleep by polysomnography (PSG)

largely confirm the subjective reports. For instance, an observer-rated study showed that administration of 10, 20, or 30 mg of THC decreased total time to fall asleep [60], and a PSG study showed both shorter sleep latency (SL) [150], and decreased time awake after sleep onset (WASO) [160]. However, other studies have not observed a decrease in sleep latency or wake time after sleep onset [75]. One possible explanation for the difference in findings may be related to disparate effects of THC (sleep promoting) and cannabidiol (a non-euphorogenic cannabinoid preferred in some medical preparations), which may increase alertness [150].

Several studies of PSG-measured sleep report increased SWS [25, 75], decreased REM sleep [74, 75, 160], and decreased REM density (e.g., number of eye movements during REM sleep) [74, 75]. However, this pattern is not always replicated [150].

In chronic users of cannabis, the effects of cannabis on objectively measured sleep are notably different. With chronic use, individuals develop tolerance to most of the effects observed in naïve users, including its sleep-inducing effects and slow-wave sleep enhancement [25, 78, 111, 163]. Sleep efficiency is similarly unimproved [163] or worsens [111]. The tolerance to REM sleep changes, however, appears to be relatively muted [75]. However, no consensus exists with respect to REM time and studies have reported decreased, no change [163], or increased [111] REM time.

PSG studies of cannabis withdrawal have demonstrated increases in sleep onset latency and wakefulness after sleep onset [27, 28, 75, 77, 78, 175] (Table 2). Total sleep time, sleep efficiency, and slow-wave sleep time is reduced [1, 27, 28, 75, 78] (Table 1), and REM sleep is increased (REM rebound) [74, 75, 77, 108, 160, 175]. Shorter REM latency has also been reported [27, 77].

Changes in the objective PSG measurements during withdrawal can start as soon as the first night of abstinence (e.g., the decrease in SWS time [74]). Changes during withdrawal are more noticeable among heavy marijuana users (marijuana use ≥ 5 times per week over the past 3 months) [27]. With continued abstinence, TST, SE, and amount of REM sleep decline (Table 2), while WASO increases. These disturbances progress over the first 2 weeks of abstinence [28, 44, 120] and persist for more than 45 days into a marijuana abstinence period [44].

There are conflicting reports with regard to REM sleep in sustained abstinence. Initially it appears that REM sleep time increases/rebounds early in abstinence, but decreases as abstinence progresses [28] (Table 2). The reason for this continued worsening of sleep with decreasing REM sleep during abstinence is unclear, but could reflect a pre-existing, underlying sleep problem and/or the long-term effects of chronic use.

Relationship between subjective and objective outcomes

As noted above, the desirable effects of cannabis on sleep are reported less frequently in chronic cannabis users compared to naïve users [91]. Chronic users also report difficulty sleeping and strange dreams among other symptoms associated with abstinence [11, 28, 43, 58, 175, 194]. These subjective findings have been correlated to longer sleep onset latency, reduced slow-wave sleep, and REM rebound observed in PSG studies [27, 198].

Clinical and laboratory correlates of subjective and objective sleep outcomes

Sleep difficulties appear to be a predisposing factor for cannabis use, and baseline sleep problems are a significant predictor of later cannabis use, doubling the risk of future use [139, 155, 166, 211, 214]. This latter finding has led some to describe cannabis use as “coping oriented use” [21].

The sleep disturbances encountered in marijuana withdrawal may play a crucial role in treatment outcomes. Higher rates of relapse have been correlated with sleep problems and other withdrawal symptoms [43]. In a study focused on military veterans, Babson et al. showed that poor sleep quality prior to the quit attempt was a predictor of higher rates of later cannabis use [19–21]. Similarly, poor sleep quality during abstinence also contributes to relapse [44, 46, 195]. Evidence from a limited number of studies suggests that objective findings, like increased periodic limb movements during abstinence, are correlated with quantity and duration of cannabis use [28].

Pharmacotherapy options targeting sleep abnormalities

Sleep disturbances associated with withdrawal improve with oral administration of THC or resumption of cannabis use [42, 44, 45, 95, 97, 108]. THC exerts a dose-dependent effect in reducing withdrawal symptoms [45], but as noted above, the beneficial effects of THC on sleep diminish with chronic use, and chronic use leads to more severe problems with sleep.

Haney et al. found the greatest benefit regarding sleep symptoms and relapse using combination therapy with lofexidine (an alpha-2 agonist) and oral THC. However they did not report any benefit from 10 days of oral THC alone [94]. Nabilone, a FDA-approved synthetic analog of THC, has the potential to reverse withdrawal-related irritability and disruptions in sleep, and promotes abstinence [92]. Nabiximols, a synthetic combination of THC and cannabidiol has a non-significant positive effect on these parameters [10].

The use of valproic acid resulted in no benefit and even some worsening of symptoms in chronic cannabis users

[95, 128]. No definitive benefits have been reported with Lithium [107], nefazodone [96], or bupropion [49, 99].

Subjective and/or objective sleep parameters have been shown to improve with the use of zolpidem [195], mirtazapine [93], gabapentin [135], and quetiapine [57], but none of these agents have conclusively reduced the relapse rate.

Cocaine

Subjective measurements

Withdrawal from cocaine is characterized by numerous subjective complaints, including sleep and sleep-related complaints. The first several days to 1 week after cocaine cessation are characterized by sleep disturbances, hypersomnia, bad dreams, depressed mood, psychomotor agitation and retardation, fatigue, and increased appetite [38, 59, 80]. With continued abstinence, however, there is subjective improvement of sleep as well as improvements in other cocaine withdrawal measures [209], with apparent normalization of subjective sleep over the course of several weeks [80].

Numerous studies have indicated an improvement in self-reported sleep quality over the first few weeks of abstinence [13, 55, 81, 138, 147, 148, 153, 172, 209], with improvements in measures such as overall sleep quality, daytime alertness, concentration/confusion, depth of sleep, and energy/fatigue. However, the possibility that such improvements may be related to acclimation to a new environment (e.g., the treatment setting [209]) and not actually reflect good sleep relative to healthy persons [55] has been raised. Possibly providing some answers to these questions, a laboratory study that included self-administration of cocaine either early or late in a 3-week period of abstinence showed that subjective sleep quality was at its worst in the first few days following cocaine use and improved with continued abstinence [148]. In addition, whereas chronic cocaine users show impairment in self-reported but quasi-objective sleep measurement like the Pittsburgh Sleep Quality Index (PSQI), visual analog scale ratings of subjective sleep quality in the third week of abstinence are no different from healthy sleepers [147]. Hence there is evidence that chronic cocaine users have chronically impaired sleep as measured by instruments like the PSQI, that self-reported sleep quality improves with continued abstinence, and that self-reported sleep quality after an extended period of abstinence is similar to that in healthy sleepers. However, this last finding may only show that chronic cocaine users' intrinsic scale for self-report of sleep quality is different from healthy sleepers, with 'good' subjective sleep in chronic cocaine users seemingly good only in comparison with the much worse sleep experience they have at other times.

Objective measurements

Although self-reported sleep improves following the initial withdrawal from cocaine, polysomnographic findings have consistently shown deterioration in sleep to insomnia-like levels in the same period [13, 81, 104, 121, 138, 145, 148, 152, 192]. The co-occurring deterioration in PSG-measured sleep and improvement in self-reported sleep quality was termed ‘occult insomnia,’ as poor sleep as measured by PSG was associated with poor performance on sleep-dependent learning and other cognitive tasks [148, 149]. These findings suggest that the PSG-measured deterioration in sleep and not the subjective improvement in sleep better reflects what is happening during abstinence from chronic cocaine use, and supports the notion that the intrinsic, subjective scale used by chronic cocaine users to report sleep quality is altered relative to healthy persons.

Sleep latency

Acute cocaine administration can increase sleep latency [104, 162, 207], but the first few days of abstinence from cocaine in chronic users is associated with short sleep latencies relative to later in abstinence [81, 121, 138, 148, 153, 192], when sleep latency may be as long as 30–60 min or more (Table 2).

Total sleep time

Total sleep time during abstinence is reduced in chronic cocaine users [147] but appears to be at its greatest sometime in the early abstinence period (first week of abstinence) in laboratory studies including cocaine self-administration [148]. Total sleep time decreases with continued abstinence (Table 2), however [81, 104, 121, 138, 147–149, 153, 162, 192, 207], with total sleep times around the third week of abstinence as low as 300–330 min despite prohibitions against daytime napping and the opportunity to sleep 8 h or more. Sleep efficiency follows a similar pattern, with insomnia-like levels apparent in the third week of abstinence [153]. Limited evidence suggests that chronic cocaine users able to maintain outpatient abstinence for as long as 54 days show some improvement in total sleep time [13].

Slow-wave sleep

Chronic cocaine users appear to have dramatically diminished slow-wave sleep time relative to age-matched healthy sleepers [13, 147] (Table 2). More limited evidence suggests that slow-wave activity is increased by cocaine self-administration earlier in the day, with a subsequent loss of slow-wave activity in the first several days of abstinence followed by a rebound over the next 2 weeks of abstinence [148]. More substantial evidence indicates that slow-wave sleep time increases modestly

from the first to the third week of abstinence [138], but at 3 weeks of abstinence is still 50 % less than age-matched healthy sleepers [13]. This deficit in slow-wave sleep generation is associated with impaired slow-wave sleep specific, sleep-dependent learning [149], and is consistent with or more profound than similar findings in chronic users of alcohol, cannabis, other stimulants, and heroin [25, 27, 175, 192] suggesting an abnormality in sleep homeostasis [145] that may be common to chronic, regular use of addictive substances.

Rem

Cocaine administration acutely suppresses REM sleep [104, 162, 207], with a subsequent rebound evident as an increase in REM sleep time and/or percent of total sleep time spent in REM (REM%), and a decrease in REM latency [81, 104, 121, 149, 153, 192, 207]. However, in chronic cocaine users, REM sleep decreases following the rebound, with low REM times observed during the second and third weeks of abstinence [13, 104, 138, 147, 149, 153, 192] (Table 2). This diminished REM sleep time is associated with cognitive consequences like poor procedural learning [149], suggesting an abnormality of REM homeostasis during abstinence from chronic use. Consistent with this idea is the observation that REM latency is higher in the third week of abstinence relative to the first [149] and at 3 weeks abstinence does not differ substantially from healthy sleepers [147] (Table 2), despite low REM sleep time.

Relationship between subjective and objective outcomes

What is now clearly shown to be a mismatch in subjective and objective experience during acute and subacute abstinence was once perceived as an inconsistency [104, 153]. One possible cause for the mismatch may be dysregulation of the homeostatic sleep drive in chronic cocaine users, wherein the ‘sleepiness’ and other negative effects of increased wakefulness are not experienced subjectively [148]. Additionally, or alternatively, the rebound in delta power after acute withdrawal [148], despite poor sleep and decreased slow-wave sleep time, may improve the subjective experience of sleep quality [122, 148]. The poor subjective experience in acute withdrawal may also be related to the decreased REM latency and increased REM sleep time, leading to increased dreaming [38, 59] and correlated with symptoms of withdrawal [13].

Clinical and laboratory correlates of subjective and objective sleep outcomes

Cognitive correlates of sleep outcomes

Chronic cocaine use is associated with various cognitive performance deficits (e.g., see [152]) that may

predict treatment retention and other outcomes [3–5]. As described briefly above, poor sleep associated with abstinence from chronic use may contribute to poor cognitive performance including decreased attention or vigilance [148, 149, 152]. The most direct associations between poor sleep and cognitive deficits, however, are observed in sleep-dependent procedural learning. In such tasks, overnight learning is strongly correlated with objective sleep measurement, such as slow-wave sleep time [189], REM time [189], and stage 2 (N2) sleep time (M. P. [202]). In chronic cocaine users, similar correlations are present; in nights with relatively normal sleep, normal sleep-dependent learning takes place, but in nights with impaired sleep, such learning is similarly impaired [148, 149]. Hence, sleep abnormalities associated with abstinence from chronic cocaine use may be responsible for significant impairment in normal, sleep-dependent learning, as well as more immediate cognitive function like attention. Intriguingly, cocaine administration is associated with temporary reversal of these deficits [148, 149, 152], further implicating such deficits in risk for relapse.

Relationship between objective measurements and clinical outcomes

Recent evidence supports the assertion that poor sleep associated with abstinence from cocaine not only impairs cognitive performance, but also contributes to increased cocaine use or relapse [13]. In this study, the homeostatic response to continued abstinence (which was measured as change in slow-wave sleep time from the first week of abstinence to the second or third week) predicted the amount of cocaine self-administered in a laboratory experiment and clinical outcome in a clinical trial. In addition, REM sleep time and total sleep time during the third week of abstinence predicted the amount of cocaine self-administered. In all cases, improvements in sleep were associated with less self-administration or better clinical outcome.

Pharmacotherapy options targeting sleep abnormalities

Although several medications such as modafinil, topiramate, tiagabine, gaboxadol and vigabatrin [145] have been suggested as potential options for targeting the sleep abnormalities associated with chronic cocaine use, few studies have examined the effects of medications on sleep in chronic cocaine users, and several of the suggested medications have potentially significant safety issues (i.e. tiagabine, gaboxadol, and vigabatrin). Hypothesizing that the REM rebound associated with initial withdrawal from cocaine was caused by dopamine insufficiency [62], Gillin et al. [81, 82] examined the effect of lisuride, a high affinity dopamine D_{2,3,4} receptor agonist, on sleep. While lisuride had the desired effect on REM

sleep (decreasing REM% and increasing REM latency), it had no effects on other withdrawal-related phenomenon [81]. In light of the clinical findings in Angarita et al. [13] and the effect of prolonged abstinence on REM sleep, it seems unlikely that reduction in REM sleep time would be beneficial during extended abstinence, but *increasing* REM to normal values could be beneficial.

Another medication that has been tested is tiagabine, a GABA-reuptake inhibitor. Since tiagabine is known to increase slow-wave sleep time, which is implicated in improved cognitive performance in sleep-restricted persons [203], it was hypothesized that tiagabine may improve slow-wave sleep time in chronic cocaine users [146]. While tiagabine had dramatic effects on slow-wave sleep time, sleep architecture appeared unnatural, with slow-wave sleep occurring throughout the sleep period. Additionally, there was no apparent benefit to total sleep time, and no consistent benefit in cognitive performance [146].

Perhaps the most promising, and most studied medication to be tested for correcting sleep abnormalities related to cocaine is modafinil. A stimulant and cognitive enhancer that appears to act at least partially through dopamine transporter blockade, modafinil appears to share some important properties with cocaine while being a relatively safe medication with low abuse potential [140]. In chronic cocaine users, modafinil has been shown to normalize slow-wave sleep time, as well as other sleep parameters [147]. Though effects of modafinil on clinical outcome have been mixed (e.g., [12, 63, 64, 176]), its effects on sleep and its pro-cognitive effects position it as the best candidate at present for a viable pharmacotherapy for cocaine use disorders.

Opioids

Subjective measurements

Short-term opioid use can cause sedation and daytime drowsiness [130, 159, 216, 217]. Dizziness and sleepiness are common side effects of opioid pain medications [41, 109]. With a stable dose, tolerance to the subjective, sedative effects of opioids develops within 2–3 days and some studies find that cognition normalizes after that [103, 129], supporting the notion of tolerance to the sedative effects. However, there is also evidence that unpleasant sedative effects, decreased alertness and increased reaction time in a variety of cognitive tasks continue to be experienced by some patients on a stable dose of narcotic medication [23, 24, 54, 181]. These differences in findings may be related to inconsistencies in how the sedative effects are defined [217].

Xiao et al. [215] studied the quality of sleep in persons with heroin use disorder on early methadone maintenance therapy (MMT) after a median of 5.4 days of

treatment [215]. Patients without pre-existing chronic sleep disturbances demonstrated lower ratings of sleep (Pittsburgh Sleep Quality Index [PSQI]) and daytime sleepiness (Epworth Sleepiness Scale [ESS]) compared to healthy sleepers. Oyefeso et al. [151] reported inadequate sleep quality and quantity as well as difficulty initiating and maintaining sleep in persons with opioid use disorders in early stages of methadone detoxification. Similar studies have shown some increased daytime drowsiness and below normal sleep measures in this patient population [113, 114, 134, 204]. After longer periods of MMT, however, there is some degree of tolerance to these effects [206], and sleep difficulty is shown to be present only in the first 6–12 months of MMT [158, 193].

There is a limited number of reports studying the effects of withdrawal and abstinence from chronic opiate use. Asaad et al. reported insomnia, hypersomnolence, increased sleep latency, and reduced sleep duration in individuals with opioid use disorder after 3 weeks of abstinence [17].

Objective measurements

Sleep architecture in healthy adults can be significantly altered even after a single dose of oral opioids [67]. Using electroencephalography (EEG) and electromyography (EMG), Kay et al. [117] reported that acute intoxication with heroin, morphine, or methadone resulted in dose-dependent enhancements in arousal during sleep–wake periods. Heroin use demonstrated a stronger effect particularly on reduction of theta waves and REM sleep [117, 204]. Morphine and methadone reduce slow-wave sleep and increase stage 2 sleep [67]. Several studies have shown that acute use of various opioids results in increased REM latency [115, 159], decreased REM sleep time [113–117, 130, 159, 180], increased stage 1 [67, 130, 180] and stage 2 sleep [67], and decreased slow-wave sleep [113–117, 159]. Acute use of opioids also leads to increased sleep latency [116, 130], increased wakefulness after sleep onset (WASO) [113–117, 130, 159, 215], and concomitant decreases in total sleep time (TST) [116, 215] and sleep efficiency (SE) [116, 159, 215].

There is a partial tolerance to the effects of opioids with some evidence for increased REM sleep time in acute use [113, 114, 130], and less pronounced changes in SWS, wakefulness, and arousal observed after chronic use. However, vocalization during REM sleep, delta bursts, and increased daytime sleepiness may be observed in this phase [204]. Tolerance to sleep problems is more prominent in MMT [113, 134, 159, 204], with evidence that persons in treatment for more than 12 months exhibit better recovery sleep following sleep deprivation than persons in shorter-term treatment [193].

Nevertheless, abnormal PSG findings are commonly reported in chronic opioid users despite development of tolerance. These abnormalities include increased sleep latency [100, 185], increased awakening [100, 113, 185, 190], decreased total sleep time [100, 185], and decreased sleep efficiency [100, 190]. Slow-wave sleep time [113, 114, 185, 190] and REM sleep are decreased compared to baseline [113, 185, 190, 205], while duration of stage 2 sleep is increased similar to acute use [190, 205]. Analysis of actigraphy data from patients with prescription opioid use disorders indicated poor sleep in terms of total sleep time, sleep efficiency, sleep latency, total time awake, and time spent moving [100].

Several studies have reported changes in patterns of sleep with progressive abstinence from opiates. At around 5–7 days of acute abstinence from chronic heroin use, Howe et al. reported decreased total sleep time, slow-wave sleep, REM, and stage 2 sleep and increased sleep latency, wake after sleep onset, and REM latency compared to healthy sleepers [101] (Table 2). During the first 3 weeks of abstinence, prolonged sleep latency, decreased sleep efficiency, decreased TST, increased arousal index, increased stage 1 and 2, and decreased slow-wave sleep (SWS) were prominent compared to healthy sleepers [17] (Table 2). After 6 weeks and up to 6 months of abstinence from methadone, there is a rebound increase in SWS and REM time to a higher level than baseline [113, 114, 134].

Relationship between subjective and objective outcomes

Using PSG data, Xiao et al. showed an inverse relationship between the Epworth Sleepiness Scale (ESS) scores and SWS time in patients with heroin use disorder who were in early methadone treatment [215]. They reported poor initial quality of sleep based on the PSQI scores which were significantly correlated with their methadone dosages [102]. PSQI score were also found to be significantly correlated with average diary-reported sleep time, subjective ratings of feeling rested, and PSG sleep efficiency in MMT patients [179]. Overall the high prevalence of sleep complaints in this population along with documented abnormal objective findings argue that these complaints are more likely to be secondary to pathology rather than sleep misperception.

Clinical and laboratory correlates of subjective and objective sleep outcomes

Opioids and sleep disordered breathing

Acute use of small doses of opioids does not appear to significantly increase the risk for increased sleep-disordered breathing [167, 180]. However, chronic opioid use has been associated with several abnormalities including nocturnal oxygen desaturations, abnormal breathing patterns, and Biot's respiration pattern

which ultimately may lead to hypercapnia and hypoxia [29, 73, 88, 126, 164, 165, 191, 201, 204, 218]. Chronic opioid treatment, particularly with extended release preparations is associated with increased risk of central and obstructive sleep apneas compared to BMI and age-matched controls [73, 88, 141, 190, 200, 201, 204, 205, 208]. Between 30 and 90 % of patients on chronic opioid therapy display signs of central apnea in a dose-dependent fashion [73, 190, 200, 201, 205]. Several studies have indicated that chronic opioid use is an independent risk factor for irregular breathing, central apneas, and hypopneas [88, 154, 200, 201]. Additional abnormalities associated with MMT include sleep-disordered breathing, lower arterial oxygen saturation and higher carbon dioxide concentration [178, 190, 205]. There is a positive correlation between the duration of MMT and plasma methadone levels with frequency of sleep apnea [190, 205].

A multivariate analysis of the relationship between demographic factors, mental health and drug use with sleep disturbances on 225 MMT patients found that depressive and anxious symptoms, greater nicotine use, bodily pain, and unemployment were all significant predictors of poorer global sleep quality [186].

Using PSG, Asaad et al. found that severity of depression in MMT patients was inversely correlated with SWS. They reported that SWS in moderate and severe depression was significantly lower than in milder depressive states. However, duration of opioid abuse or type of opioid did not show a significant correlation with the abnormalities in the sleep profile [17].

Relationship between subjective measurements and clinical outcomes

Peles et al. [156] used a logistic regression model and showed that a higher methadone dose (defined as greater than 120 mg/day) was associated with poor sleep quality, higher rate of sleep disturbance, more frequent use of sleeping medications, and higher rate of daytime dysfunction [156]. However in a later study (2009), they found no direct correlation between the methadone dose and worse objective and perceived sleep parameters. Rather they suggested that duration and intensity of opioid abuse before admission to MMT was directly correlated with sleep abnormalities [157].

Quality of sleep in substance users who are trying to quit plays an important role in predicting the treatment outcome and poor sleep quality is associated with higher risk of relapse [40, 204]. Predictive factors for abstinence 1 month after detoxification with naltrexone may include sleeping problems upon discharge and any changes in sleeping problems [66]. In MMT patients, psychiatric disorders, greater nicotine and benzodiazepine use,

bodily pain, and unemployment are associated with poorer global sleep quality [156, 186].

Relationship between objective measurements and clinical outcomes

Using PSG, Peles et al. evaluated patients with heroin use disorder who were being treated with high and low dose methadone [157]. Of the objective sleep indices, percentage of non-REM deep sleep (i.e. SWS) inversely correlated with number of years of opioid abuse. They found that a lower percentage of SWS and more years of opioid abuse were observed in the group who received higher methadone dose during MMT.

Positive effects of opioids on sleep

Judicious use of opioid medications might improve pain-related sleep disorders [14, 30]. Subjective reports of improved sleep after pain control with extended-release morphine sulfate use to treat patients with chronic hip or knee arthritis are backed by objective evidence obtained from PSG indicating better sleep quality [170]. Opioids have also been used to treat a sleep disorder known as periodic limb movement (PLMS), which is often associated with restless legs syndrome [144].

Pharmacotherapy options targeting sleep abnormalities

Modifiable psychological and medical risk factors associated with sleep disturbance should be identified and corrected in order to improve quality of life in drug treatment. Treatment of sleep disorders among MMT patients, particularly in those with psychiatric disorders, benzodiazepine abuse, chronic pain, and patients who are on high methadone dose is of crucial importance.

Methadone

Methadone maintenance is widely used and a standard pharmacotherapy for treating patients with opioid use disorders [18, 68, 71, 197, 220]. Chronic methadone use is more commonly associated with tolerance to the sleep problems compared to other opioids [113, 134, 159, 204]. However, more than three-quarters of persons receiving methadone maintenance therapy (MMT) still report sleep complaints [151, 156, 186]. This is complicated by the fact that about 50 % of MMT patients report use of both illicit drugs and legal medications to help with sleep [156, 186]. Methadone and electrostimulation (ES) have been used to treat insomnia in the first 30 days of opioid withdrawal [84]. In the first 2 weeks of withdrawal patients treated with electrostimulation had shorter sleep time and more awakenings than patients receiving methadone. They also found that subjects in the ES group who remained in treatment experienced more sleep disturbance than those who dropped out prematurely. Overall

methadone and ES were not efficient in treating insomnia associated with withdrawal. Stein et al. tested whether trazodone (50 mg/night), one of the most commonly prescribed medications for treatment of insomnia, improved sleep among methadone-maintained persons with PSQI score of six or higher [187]. They found that trazodone did not improve subjective or objective sleep problems in this group of patients.

Buprenorphine

Buprenorphine was FDA approved as a pharmacotherapy for opioid use disorders in 2002. Buprenorphine has the advantage of being available from office-based practices [131]. There are limited numbers of studies looking at the effect of buprenorphine on sleep. One study suggests that buprenorphine is comparable to methadone in improving sleep quality in patients involved in long-term treatment [133]. In another study, forty-two patients with opiate use disorder were treated with either methadone or buprenorphine and gradually tapered down over the course of 2–3 weeks. Buprenorphine-treated patients had 2.5 % lower sleep efficiency and 9 % shorter actual sleep time. These significant group differences were most pronounced with the lowest doses toward the late withdrawal phase [161]. The time course of tapering buprenorphine during detoxification might also play a role in the quantity of sleep. A randomized controlled trial of buprenorphine for detoxification from prescription opioid use evaluated sleep time among patients assigned to receive 1, 2, and 4-week buprenorphine tapers. The 4-week taper group reported significantly less loss of sleep compared to the other groups [70].

In a study of 70 patients with chronic opioid use, the effect of buprenorphine on sleep disordered breathing was measured polysomnographically [72]. Patients in this study tended to be young (mean age of 31.8) and non-obese (mean body mass index 24.9 ± 5.9). However, treatment with buprenorphine was associated with mild to severe sleep-disordered breathing in this population, with a substantial rate of associated hypoxemia [72].

Although information on the effect of other medications on sleep in chronic opiate users is limited, Srisurapanont and Jarusuraisin [184] explored the effect of amitriptyline (57.7 ± 12 /night) versus lorazepam (2.1 ± 0.5 /night) to treat insomnia in 27 patients with opioid withdrawal in a randomized double-blind study [184]. The Sleep Evaluation Questionnaire and three insomnia items of the Hamilton Depression Rating Scale were used to assess sleep. All aspects of sleep (including ease of getting to sleep, perceived quality of sleep, integrity of early morning behavior following wakefulness and Hamilton Depression Rating Scale insomnia items), except for ease of awakening from sleep, were not significantly different in the two treatment

groups. These findings suggest that apart from the hangover effect, amitriptyline is as effective as lorazepam in the treatment of opioid-withdrawal insomnia.

Conclusion

Overwhelming evidence points to chronic alterations in sleep from chronic use of addictive substances that may be distinct from some or all of the acute effects of those substances. Interestingly, the effects of chronic use on sleep are similar among both CNS stimulants and depressants. Decreased sleep time, increased sleep latency and wake time after sleep onset, and deficiency in slow-wave sleep generation appear to be common to chronic use of alcohol, cocaine, cannabis, and opiates. REM sleep is also affected by acute and chronic use, but may be more sensitive to the pattern or quantity of recent use and time from last use, as results vary more among studies. Also linking these abnormalities are connections with ongoing use and relapse. However, treatment with typical sleep promoting agents that increase sleep time or efficiency by increasing light sleep may be counterproductive. Agents that address deficiency in slow-wave sleep generation and alterations in REM sleep may prove to be more useful in addressing the connection between chronically-altered sleep physiology and ongoing use and relapse, but substantial research still needs to be done to explore this possibility.

Authors' contributions

GA performed the initial literature review and drafted the introduction and alcohol sections and coordinated the work of NE and SH. NE drafted the cannabis and opiate sections. SH drafted the cocaine section. PM oversaw the work of the other authors and re-worked the manuscript into its final form, contributing to each section. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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References

1. Adams PM, Barratt ES. Effect of chronic marijuana administration of stages of primate sleep-wakefulness. *Biol Psychiatry*. 1975;10(3):315–22.
2. Adamson J, Burdick JA. Sleep of dry alcoholics. *Arch Gen Psychiatry*. 1973;28(1):146–9.
3. Aharonovich E, Amrhein PC, Bisaga A, Nunes EV, Hasin DS. Cognition, commitment language, and behavioral change among cocaine-dependent patients. *Psychol Addict Behav*. 2008;22(4):557–62. doi:10.1037/a0012971.

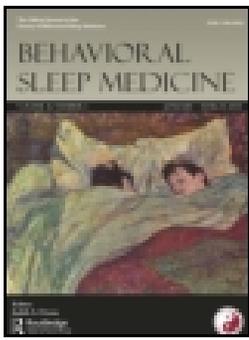
4. Aharonovich E, Hasin DS, Brooks AC, Liu X, Bisaga A, Nunes EV. Cognitive deficits predict low treatment retention in cocaine dependent patients. *Drug Alcohol Depend*. 2006;81(3):313–22. doi:[10.1016/j.drugalcdep.2005.08.003](https://doi.org/10.1016/j.drugalcdep.2005.08.003).
5. Aharonovich E, Nunes E, Hasin D. Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment. *Drug Alcohol Depend*. 2003;71(2):207–11.
6. Aldrich MS, Shipley JE, Tandon R, Kroll PD, Brower KJ. Sleep-disordered breathing in alcoholics: association with age. *Alcohol Clin Exp Res*. 1993;17(6):1179–83.
7. Allen RP, Faillace LA, Wagman A. Recovery time for alcoholics after prolonged alcohol intoxication. *Johns Hopkins Med J*. 1971;128(3):158–64.
8. Allen RP, Wagman AM. Do sleep patterns relate to the desire for alcohol? *Adv Exp Med Biol*. 1975;59:495–508.
9. Allen RP, Wagman AM, Funderburk FR, Wells DT. Slow wave sleep: a predictor of individual differences in response to drinking? *Biol Psychiatry*. 1980;15(2):345–8.
10. Allsop DJ, Copeland J, Lintzeris N, Dunlop AJ, Montebello M, Sadler C, et al. Nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. *JAMA Psychiatry*. 2014;71(3):281–91. doi:[10.1001/jamapsychiatry.2013.3947](https://doi.org/10.1001/jamapsychiatry.2013.3947).
11. Allsop DJ, Norberg MM, Copeland J, Fu S, Budney AJ. The Cannabis Withdrawal Scale development: patterns and predictors of cannabis withdrawal and distress. *Drug Alcohol Depend*. 2011;119(1–2):123–9. doi:[10.1016/j.drugalcdep.2011.06.003](https://doi.org/10.1016/j.drugalcdep.2011.06.003).
12. Anderson AL, Reid MS, Li SH, Holmes T, Shemanski L, Slee A, et al. Modafinil for the treatment of cocaine dependence. *Drug Alcohol Depend*. 2009;104(1–2):133–9. doi:[10.1016/j.drugalcdep.2009.04.015](https://doi.org/10.1016/j.drugalcdep.2009.04.015).
13. Angarita GA, Canavan SV, Forselius E, Bessette A, Pittman B, Morgan PT. Abstinence-related changes in sleep during treatment for cocaine dependence. *Drug Alcohol Depend*. 2014;134:343–7. doi:[10.1016/j.drugalcdep.2013.11.007](https://doi.org/10.1016/j.drugalcdep.2013.11.007).
14. Argoff CE, Silvershein DI. A comparison of long- and short-acting opioids for the treatment of chronic noncancer pain: tailoring therapy to meet patient needs. *Mayo Clin Proc*. 2009;84(7):602–12. doi:[10.1016/S0025-6196\(11\)60749-0](https://doi.org/10.1016/S0025-6196(11)60749-0).
15. Arnedt JT, Conroy DA, Armitage R, Brower KJ. Cognitive-behavioral therapy for insomnia in alcohol dependent patients: a randomized controlled pilot trial. *Behav Res Ther*. 2011;49(4):227–33. doi:[10.1016/j.brat.2011.02.003](https://doi.org/10.1016/j.brat.2011.02.003).
16. Arnedt JT, Conroy DA, Brower KJ. Treatment options for sleep disturbances during alcohol recovery. *J Addict Dis*. 2007;26(4):41–54. doi:[10.1300/J069v26n04_06](https://doi.org/10.1300/J069v26n04_06).
17. Asaad T, Ghanem M, Abdel Samee A, El-Habiby M. Sleep profile in patients with chronic opioid abuse: a polysomnographic evaluation in an Egyptian sample. *Addict Disord Their Treat*. 2011;10(1):21–8.
18. Athanasos P, Smith CS, White JM, Somogyi AA, Bochner F, Ling W. Methadone maintenance patients are cross-tolerant to the antinociceptive effects of very high plasma morphine concentrations. *Pain*. 2006;120(3):267–75. doi:[10.1016/j.pain.2005.11.005](https://doi.org/10.1016/j.pain.2005.11.005).
19. Babson KA, Boden MT, Bonn-Miller MO. The impact of perceived sleep quality and sleep efficiency/duration on cannabis use during a self-guided quit attempt. *Addict Behav*. 2013;38(11):2707–13. doi:[10.1016/j.addbeh.2013.06.012](https://doi.org/10.1016/j.addbeh.2013.06.012).
20. Babson KA, Boden MT, Bonn-Miller MO. Sleep quality moderates the relation between depression symptoms and problematic cannabis use among medical cannabis users. *Am J Drug Alcohol Abuse*. 2013;39(3):211–6. doi:[10.3109/00952990.2013.788183](https://doi.org/10.3109/00952990.2013.788183).
21. Babson KA, Boden MT, Harris AH, Stickle TR, Bonn-Miller MO. Poor sleep quality as a risk factor for lapse following a cannabis quit attempt. *J Subst Abuse Treat*. 2013;44(4):438–43. doi:[10.1016/j.jsat.2012.08.224](https://doi.org/10.1016/j.jsat.2012.08.224).
22. Baekeland F, Lundwall L, Shanahan TJ, Kissin B. Clinical correlates of reported sleep disturbance in alcoholics. *Q J Stud Alcohol*. 1974;35(4):1230–41.
23. Banning A, Sjogren P. Cerebral effects of long-term oral opioids in cancer patients measured by continuous reaction time. *Clin J Pain*. 1990;6(2):91–5.
24. Banning A, Sjogren P, Kaiser F. Reaction time in cancer patients receiving peripherally acting analgesics alone or in combination with opioids. *Acta Anaesthesiol Scand*. 1992;36(5):480–2.
25. Barratt ES, Beaver W, White R. The effects of marijuana on human sleep patterns. *Biol Psychiatry*. 1974;8(1):47–54.
26. Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders. A meta-analysis. *Arch Gen Psychiatry*. 1992;49(8):651–68 (**discussion 669–670**).
27. Bolla KI, Lesage SR, Gamaldo CE, Neubauer DN, Funderburk FR, Cadet JL, et al. Sleep disturbance in heavy marijuana users. *Sleep*. 2008;31(6):901–8.
28. Bolla KI, Lesage SR, Gamaldo CE, Neubauer DN, Wang NY, Funderburk FR, et al. Polysomnogram changes in marijuana users who report sleep disturbances during prior abstinence. *Sleep Med*. 2010;11(9):882–9. doi:[10.1016/j.sleep.2010.02.013](https://doi.org/10.1016/j.sleep.2010.02.013).
29. Bouillon T, Bruhn J, Roepcke H, Hoef A. Opioid-induced respiratory depression is associated with increased tidal volume variability. *Eur J Anaesthesiol*. 2003;20(2):127–33.
30. Brennan MJ, Lieberman JA 3rd. Sleep disturbances in patients with chronic pain: effectively managing opioid analgesia to improve outcomes. *Curr Med Res Opin*. 2009;25(5):1045–55. doi:[10.1185/03007990902797790](https://doi.org/10.1185/03007990902797790).
31. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry*. 1996;39(6):411–8.
32. Brower KJ. Alcohol's effects on sleep in alcoholics. *Alcohol Res Health*. 2001;25(2):110–25.
33. Brower KJ. Insomnia, alcoholism and relapse. *Sleep Med Rev*. 2003;7(6):523–39.
34. Brower KJ, Aldrich MS, Hall JM. Polysomnographic and subjective sleep predictors of alcoholic relapse. *Alcohol Clin Exp Res*. 1998;22(8):1864–71.
35. Brower KJ, Aldrich MS, Robinson EA, Zucker RA, Greden JF. Insomnia, self-medication, and relapse to alcoholism. *Am J Psychiatry*. 2001;158(3):399–404.
36. Brower KJ, Conroy DA, Kurth ME, Anderson BJ, Stein MD. Ramelteon and improved insomnia in alcohol-dependent patients: a case series. *J Clin Sleep Med*. 2011;7(3):274–5. doi:[10.5664/JCSM.1070](https://doi.org/10.5664/JCSM.1070).
37. Brower KJ, Krentzman A, Robinson EA. Persistent insomnia, abstinence, and moderate drinking in alcohol-dependent individuals. *Am J Addict*. 2011;20(5):435–40. doi:[10.1111/j.1521-0391.2011.00152.x](https://doi.org/10.1111/j.1521-0391.2011.00152.x).
38. Brower KJ, Maddahian E, Blow FC, Beresford TP. A comparison of self-reported symptoms and DSM-III-R criteria for cocaine withdrawal. *Am J Drug Alcohol Abuse*. 1988;14(3):347–56.
39. Brower KJ, Myra Kim H, Strobbe S, Karam-Hage MA, Consens F, Zucker RA. A randomized double-blind pilot trial of gabapentin versus placebo to treat alcohol dependence and comorbid insomnia. *Alcohol Clin Exp Res*. 2008;32(8):1429–38. doi:[10.1111/j.1530-0277.2008.00706.x](https://doi.org/10.1111/j.1530-0277.2008.00706.x).
40. Brower KJ, Perron BE. Sleep disturbance as a universal risk factor for relapse in addictions to psychoactive substances. *Med Hypotheses*. 2010;74(5):928–33. doi:[10.1016/j.mehy.2009.10.020](https://doi.org/10.1016/j.mehy.2009.10.020).
41. Bruera E, Macmillan K, Hanson J, MacDonald RN. The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. *Pain*. 1989;39(1):13–6.
42. Budney AJ, Hughes JR, Moore BA, Novy PL. Marijuana abstinence effects in marijuana smokers maintained in their home environment. *Arch Gen Psychiatry*. 2001;58(10):917–24.
43. Budney AJ, Hughes JR, Moore BA, Vandrey R. Review of the validity and significance of cannabis withdrawal syndrome. *Am J Psychiatry*. 2004;161(11):1967–77. doi:[10.1176/appi.ajp.161.11.1967](https://doi.org/10.1176/appi.ajp.161.11.1967).
44. Budney AJ, Moore BA, Vandrey RG, Hughes JR. The time course and significance of cannabis withdrawal. *J Abnorm Psychol*. 2003;112(3):393–402.
45. Budney AJ, Vandrey RG, Hughes JR, Moore BA, Bahrenburg B. Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. *Drug Alcohol Depend*. 2007;86(1):22–9. doi:[10.1016/j.drugalcdep.2006.04.014](https://doi.org/10.1016/j.drugalcdep.2006.04.014).
46. Budney AJ, Vandrey RG, Hughes JR, Thostenson JD, Bursac Z. Comparison of cannabis and tobacco withdrawal: severity and contribution to relapse. *J Subst Abuse Treat*. 2008;35(4):362–8. doi:[10.1016/j.jsat.2008.01.002](https://doi.org/10.1016/j.jsat.2008.01.002).
47. Burke CK, Peirce JM, Kidorf MS, Neubauer D, Punjabi NM, Stoller KB, et al. Sleep problems reported by patients entering opioid agonist

- treatment. *J Subst Abuse Treat.* 2008;35(3):328–33. doi:[10.1016/j.jsat.2007.10.003](https://doi.org/10.1016/j.jsat.2007.10.003).
48. Caetano R, Clark CL, Greenfield TK. Prevalence, trends, and incidence of alcohol withdrawal symptoms: analysis of general population and clinical samples. *Alcohol Health Res World.* 1998;22(1):73–9.
 49. Carpenter KM, McDowell D, Brooks DJ, Cheng WY, Levin FR. A preliminary trial: double-blind comparison of nefazodone, bupropion-SR, and placebo in the treatment of cannabis dependence. *Am J Addict.* 2009;18(1):53–64. doi:[10.1080/10550490802408936](https://doi.org/10.1080/10550490802408936).
 50. Chait LD. Subjective and behavioral effects of marijuana the morning after smoking. *Psychopharmacology.* 1990;100(3):328–33.
 51. Chait LD, Perry JL. Acute and residual effects of alcohol and marijuana, alone and in combination, on mood and performance. *Psychopharmacology.* 1994;115(3):340–9.
 52. Chait LD, Zacny JP. Reinforcing and subjective effects of oral delta 9-THC and smoked marijuana in humans. *Psychopharmacology.* 1992;107(2–3):255–62.
 53. Chakravorty S, Hanlon AL, Kuna ST, Ross RJ, Kampman KM, Witte LM, et al. The effects of quetiapine on sleep in recovering alcohol-dependent subjects: a pilot study. *J Clin Psychopharmacol.* 2014;34(3):350–4. doi:[10.1097/JCP.0000000000000130](https://doi.org/10.1097/JCP.0000000000000130).
 54. Clemons M, Regnard C, Appleton T. Alertness, cognition and morphine in patients with advanced cancer. *Cancer Treat Rev.* 1996;22(6):451–68.
 55. Coffey SF, Dansky BS, Carrigan MH, Brady KT. Acute and protracted cocaine abstinence in an outpatient population: a prospective study of mood, sleep and withdrawal symptoms. *Drug Alcohol Depend.* 2000;59(3):277–86.
 56. Conroy DA, Arnedt JT. Sleep and substance use disorders: an update. *Curr Psychiatry Rep.* 2014;16(10):487. doi:[10.1007/s11920-014-0487-3](https://doi.org/10.1007/s11920-014-0487-3).
 57. Cooper ZD, Foltin RW, Hart CL, Vosburg SK, Comer SD, Haney M. A human laboratory study investigating the effects of quetiapine on marijuana withdrawal and relapse in daily marijuana smokers. *Addict Biol.* 2013;18(6):993–1002. doi:[10.1111/j.1369-1600.2012.00461.x](https://doi.org/10.1111/j.1369-1600.2012.00461.x).
 58. Copersino ML, Boyd SJ, Tashkin DP, Huestis MA, Heishman SJ, Dermand JC, et al. Cannabis withdrawal among non-treatment-seeking adult cannabis users. *Am J Addict.* 2006;15(1):8–14. doi:[10.1080/10550490500418997](https://doi.org/10.1080/10550490500418997).
 59. Cottler LB, Shillington AM, Compton WM 3rd, Mager D, Spitznagel EL. Subjective reports of withdrawal among cocaine users: recommendations for DSM-IV. *Drug Alcohol Depend.* 1993;33(2):97–104.
 60. Cousens K, DiMascio A. (-) Delta 9 THC as an hypnotic. An experimental study of three dose levels. *Psychopharmacologia.* 1973;33(4):355–64.
 61. Crowley TJ, Macdonald MJ, Whitmore EA, Mikulich SK. Cannabis dependence, withdrawal, and reinforcing effects among adolescents with conduct symptoms and substance use disorders. *Drug Alcohol Depend.* 1998;50(1):27–37.
 62. Dackis CA, Gold MS. New concepts in cocaine addiction: the dopamine depletion hypothesis. *Neurosci Biobehav Rev.* 1985;9(3):469–77.
 63. Dackis CA, Kampman KM, Lynch KG, Pettinati HM, O'Brien CP. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *Neuropsychopharmacology.* 2005;30(1):205–11. doi:[10.1038/sj.npp.1300600](https://doi.org/10.1038/sj.npp.1300600).
 64. Dackis CA, Kampman KM, Lynch KG, Plebani JG, Pettinati HM, Sparkman T, O'Brien CP. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *J Subst Abuse Treat.* 2012;43(3):303–12. doi:[10.1016/j.jsat.2011.12.014](https://doi.org/10.1016/j.jsat.2011.12.014).
 65. Dijk DJ. Slow-wave sleep deficiency and enhancement: implications for insomnia and its management. *World J Biol Psychiatry.* 2010;11(Suppl 1):22–8. doi:[10.3109/15622971003637645](https://doi.org/10.3109/15622971003637645).
 66. Dijkstra BA, De Jong CA, Krabbe PF, van der Staak CP. Prediction of abstinence in opioid-dependent patients. *J Addict Med.* 2008;2(4):194–201. doi:[10.1097/ADM.0b013e31818a6596](https://doi.org/10.1097/ADM.0b013e31818a6596).
 67. Dimsdale JE, Norman D, DeJardin D, Wallace MS. The effect of opioids on sleep architecture. *J Clin Sleep Med.* 2007;3(1):33–6.
 68. Doversy M, Somogyi AA, White JM, Bochner F, Beare CH, Menelaou A, Ling W. Methadone maintenance patients are cross-tolerant to the antinociceptive effects of morphine. *Pain.* 2001;93(2):155–63.
 69. Drummond SP, Gillin JC, Smith TL, DeModena A. The sleep of abstinent pure primary alcoholic patients: natural course and relationship to relapse. *Alcohol Clin Exp Res.* 1998;22(8):1796–802.
 70. Dunn KE, Saulsgiver KA, Miller ME, Nuzzo PA, Sigmon SC. Characterizing opioid withdrawal during double-blind buprenorphine detoxification. *Drug Alcohol Depend.* 2015;151:47–55. doi:[10.1016/j.drugalcdep.2015.02.033](https://doi.org/10.1016/j.drugalcdep.2015.02.033).
 71. Eugenio KR. Profound morphine tolerance following high-dose methadone therapy. *J Pain Palliat Care Pharmacother.* 2004;18(4):47–54.
 72. Farney RJ, McDonald AM, Boyle KM, Snow GL, Nuttall RT, Coudreaux MF, et al. Sleep disordered breathing in patients receiving therapy with buprenorphine/naloxone. *Eur Respir J.* 2013;42(2):394–403. doi:[10.1183/09031936.00120012](https://doi.org/10.1183/09031936.00120012).
 73. Farney RJ, Walker JM, Cloward TV, Rhondeau S. Sleep-disordered breathing associated with long-term opioid therapy. *Chest.* 2003;123(2):632–9.
 74. Feinberg I, Jones R, Walker J, Cavness C, Floyd T. Effects of marijuana extract and tetrahydrocannabinol on electroencephalographic sleep patterns. *Clin Pharmacol Ther.* 1976;19(6):782–94.
 75. Feinberg I, Jones R, Walker JM, Cavness C, March J. Effects of high dosage delta-9-tetrahydrocannabinol on sleep patterns in man. *Clin Pharmacol Ther.* 1975;17(4):458–66.
 76. Foster JH, Peters TJ. Impaired sleep in alcohol misusers and dependent alcoholics and the impact upon outcome. *Alcohol Clin Exp Res.* 1999;23(6):1044–51.
 77. Freeman FR. Effects of marijuana on sleeping states. *JAMA.* 1972;220(10):1364–5.
 78. Freeman FR. The effect of chronically administered delta-9-tetrahydrocannabinol upon the polygraphically monitored sleep of normal volunteers. *Drug Alcohol Depend.* 1982;10(4):345–53.
 79. Friedmann PD, Rose JS, Swift R, Stout RL, Millman RP, Stein MD. Trazodone for sleep disturbance after alcohol detoxification: a double-blind, placebo-controlled trial. *Alcohol Clin Exp Res.* 2008;32(9):1652–60. doi:[10.1111/j.1530-0277.2008.00742.x](https://doi.org/10.1111/j.1530-0277.2008.00742.x).
 80. Gawin FH, Kleber HD. Abstinence symptomatology and psychiatric diagnosis in cocaine abusers. Clinical observations. *Arch Gen Psychiatry.* 1986;43(2):107–13.
 81. Gillin JC, Pulvirenti L, Withers N, Golshan S, Koob G. The effects of lisuride on mood and sleep during acute withdrawal in stimulant abusers: a preliminary report. *Biol Psychiatry.* 1994;35(11):843–9.
 82. Gillin JC, Smith TL, Irwin M, Butters N, Demodena A, Schuckit M. Increased pressure for rapid eye movement sleep at time of hospital admission predicts relapse in nondepressed patients with primary alcoholism at 3-month follow-up. *Arch Gen Psychiatry.* 1994;51(3):189–97.
 83. Gillin JC, Smith TL, Irwin M, Kripke DF, Brown S, Schuckit M. Short REM latency in primary alcoholic patients with secondary depression. *Am J Psychiatry.* 1990;147(1):106–9.
 84. Gossop M, Bradley B. Insomnia among addicts during supervised withdrawal from opiates: a comparison of oral methadone and electrostimulation. *Drug Alcohol Depend.* 1984;13(2):191–8.
 85. Gross MM, Goodenough DR, Hastey J, Lewis E. Experimental study of sleep in chronic alcoholics before, during, and after four days of heavy drinking with a nondrinking comparison. *Ann NY Acad Sci.* 1973;215:254–65.
 86. Gross MM, Hastey JM. The relation between baseline slow wave sleep and the slow wave sleep response to alcohol in alcoholics. *Adv Exp Med Biol.* 1975;59:467–75.
 87. Grosshans M, Mutschler J, Luderer M, Mann K, Kiefer F. Agomelatine is effective in reducing insomnia in abstinent alcohol-dependent patients. *Clin Neuropharmacol.* 2014;37(1):6–8. doi:[10.1097/WNF.0000000000000007](https://doi.org/10.1097/WNF.0000000000000007).
 88. Guilleminault C, Cao M, Yue HJ, Chawla P. Obstructive sleep apnea and chronic opioid use. *Lung.* 2010;188(6):459–68. doi:[10.1007/s00408-010-9254-3](https://doi.org/10.1007/s00408-010-9254-3).
 89. Haario P, Rahkonen O, Laaksonen M, Lahelma E, Lallukka T. Bidirectional associations between insomnia symptoms and unhealthy behaviours. *J Sleep Res.* 2013;22(1):89–95. doi:[10.1111/j.1365-2869.2012.01043.x](https://doi.org/10.1111/j.1365-2869.2012.01043.x).
 90. Hajak G, Muller WE, Wittchen HU, Pittrow D, Kirch W. Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. *Addiction.* 2003;98(10):1371–8.
 91. Halikas JA, Weller RA, Morse CL, Hoffmann RG. A longitudinal study of marijuana effects. *Int J Addict.* 1985;20(5):701–11.
 92. Haney M, Cooper ZD, Bedi G, Vosburg SK, Comer SD, Foltin RW. Nabilone decreases marijuana withdrawal and a laboratory measure

- of marijuana relapse. *Neuropsychopharmacology*. 2013;38(8):1557–65. doi:10.1038/npp.2013.54.
93. Haney M, Hart CL, Vosburg SK, Comer SD, Reed SC, Cooper ZD, Foltin RW. Effects of baclofen and mirtazapine on a laboratory model of marijuana withdrawal and relapse. *Psychopharmacology*. 2010;211(2):233–44. doi:10.1007/s00213-010-1888-6.
 94. Haney M, Hart CL, Vosburg SK, Comer SD, Reed SC, Foltin RW. Effects of THC and lofexidine in a human laboratory model of marijuana withdrawal and relapse. *Psychopharmacology*. 2008;197(1):157–68. doi:10.1007/s00213-007-1020-8.
 95. Haney M, Hart CL, Vosburg SK, Nasser J, Bennett A, Zubaran C, Foltin RW. Marijuana withdrawal in humans: effects of oral THC or divalproex. *Neuropsychopharmacology*. 2004;29(1):158–70. doi:10.1038/sj.npp.1300310.
 96. Haney M, Hart CL, Ward AS, Foltin RW. Nefazodone decreases anxiety during marijuana withdrawal in humans. *Psychopharmacology*. 2003;165(2):157–65. doi:10.1007/s00213-002-1210-3.
 97. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology*. 1999;141(4):385–94.
 98. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology*. 1999;141(4):395–404.
 99. Haney M, Ward AS, Comer SD, Hart CL, Foltin RW, Fischman MW. Bupropion SR worsens mood during marijuana withdrawal in humans. *Psychopharmacology*. 2001;155(2):171–9.
 100. Hartwell EE, Pfeifer JG, McCauley JL, Moran-Santa Maria M, Back SE. Sleep disturbances and pain among individuals with prescription opioid dependence. *Addict Behav*. 2014;39(10):1537–42. doi:10.1016/j.addbeh.2014.05.025.
 101. Howe RC, Hegge FW, Phillips JL. Acute heroin abstinence in man: I. Changes in behavior and sleep. *Drug Alcohol Depend*. 1980;5(5):341–56.
 102. Hsu WY, Chiu NY, Liu JT, Wang CH, Chang TG, Liao YC, Kuo PI. Sleep quality in heroin addicts under methadone maintenance treatment. *Acta Neuropsychiatr*. 2012;24(6):356–60. doi:10.1111/j.1601-5215.2011.00628.x.
 103. Jacox A, Carr DB, Payne R. New clinical-practice guidelines for the management of pain in patients with cancer. *N Engl J Med*. 1994;330(9):651–5. doi:10.1056/NEJM199403033300926.
 104. Johanson CE, Roehrs T, Schuh K, Warbasse L. The effects of cocaine on mood and sleep in cocaine-dependent males. *Exp Clin Psychopharmacol*. 1999;7(4):338–46.
 105. Johnson EO, Breslau N. Sleep problems and substance use in adolescence. *Drug Alcohol Depend*. 2001;64(1):1–7.
 106. Johnson LC, Burdick JA, Smith J. Sleep during alcohol intake and withdrawal in the chronic alcoholic. *Arch Gen Psychiatry*. 1970;22(5):406–18.
 107. Johnston J, Lintzeris N, Allsop DJ, Suraev A, Booth J, Carson DS, et al. Lithium carbonate in the management of cannabis withdrawal: a randomized placebo-controlled trial in an inpatient setting. *Psychopharmacology*. 2014. doi:10.1007/s00213-014-3611-5.
 108. Jones RT, Benowitz N, Bachman J. Clinical studies of cannabis tolerance and dependence. *Ann NY Acad Sci*. 1976;282:221–39.
 109. Kantor TG, Hopper M, Laska E. Adverse effects of commonly ordered oral narcotics. *J Clin Pharmacol*. 1981;21(1):1–8.
 110. Kaplan KA, McQuaid J, Batki SL, Rosenlicht N. Behavioral treatment of insomnia in early recovery. *J Addict Med*. 2014;8(6):395–8. doi:10.1097/ADM.000000000000058.
 111. Karacan I, Fernandez-Salas A, Coggins WJ, Carter WE, Williams RL, Thornby JI, et al. Sleep electroencephalographic-electrooculographic characteristics of chronic marijuana users: part I. *Ann NY Acad Sci*. 1976;282:348–74.
 112. Karam-Hage M, Brower KJ. Open pilot study of gabapentin versus trazodone to treat insomnia in alcoholic outpatients. *Psychiatry Clin Neurosci*. 2003;57(5):542–4. doi:10.1046/j.1440-1819.2003.01161.x.
 113. Kay DC. Human sleep and EEG through a cycle of methadone dependence. *Electroencephalogr Clin Neurophysiol*. 1975;38(1):35–43.
 114. Kay DC. Human sleep during chronic morphine intoxication. *Psychopharmacologia*. 1975;44(2):117–24.
 115. Kay DC, Eisenstein RB, Jasinski DR. Morphine effects on human REM state, waking state and NREM sleep. *Psychopharmacologia*. 1969;14(5):404–16.
 116. Kay DC, Pickworth WB, Neider GL. Morphine-like insomnia from heroin in nondependent human addicts. *Br J Clin Pharmacol*. 1981;11(2):159–69.
 117. Kay DC, Pickworth WB, Neider GL, Falcone D, Fishman PM, Othmer E. Opioid effects on computer-derived sleep and EEG parameters in nondependent human addicts. *Sleep*. 1979;2(2):175–91.
 118. Knowles JB, Laverty SG, Kuechler HA. Effects on REM sleep. *Q J Stud Alcohol*. 1968;29(2):342–9.
 119. Kolla BP, Mansukhani MP, Schneekloth T. Pharmacological treatment of insomnia in alcohol recovery: a systematic review. *Alcohol Alcohol*. 2011;46(5):578–85. doi:10.1093/alcalc/agr073.
 120. Kouri EM, Pope HG Jr. Abstinence symptoms during withdrawal from chronic marijuana use. *Exp Clin Psychopharmacol*. 2000;8(4):483–92.
 121. Kowatch RA, Schnoll SS, Knisely JS, Green D, Elswick RK. Electroencephalographic sleep and mood during cocaine withdrawal. *J Addict Dis*. 1992;11(4):21–45. doi:10.1300/J069v11n04_03.
 122. Krystal AD, Edinger JD, Wohlgemuth WK, Marsh GR. NREM sleep EEG frequency spectral correlates of sleep complaints in primary insomnia subtypes. *Sleep*. 2002;25(6):630–40.
 123. Kuhlwein E, Hauger RL, Irwin MR. Abnormal nocturnal melatonin secretion and disordered sleep in abstinent alcoholics. *Biol Psychiatry*. 2003;54(12):1437–43.
 124. Landolt HP, Gillin JC. Sleep abnormalities during abstinence in alcohol-dependent patients. Aetiology and management. *CNS Drugs*. 2001;15(5):413–25.
 125. Le Bon O, Murphy JR, Staner L, Hoffmann G, Kormoss N, Kentos M, et al. Double-blind, placebo-controlled study of the efficacy of trazodone in alcohol post-withdrawal syndrome: polysomnographic and clinical evaluations. *J Clin Psychopharmacol*. 2003;23(4):377–83. doi:10.1097/01.jcp.0000085411.08426.d3.
 126. Leino K, Mildh L, Lertola K, Seppala T, Kirvela O. Time course of changes in breathing pattern in morphine- and oxycodone-induced respiratory depression. *Anaesthesia*. 1999;54(9):835–40.
 127. Lester BK, Rundell OH, Cowden LC, Williams HL. Chronic alcoholism, alcohol and sleep. In: Gross MM, editor. *Alcohol intoxication and withdrawal I*. New York: Plenum Press; 1973. p. 261–79.
 128. Levin FR, McDowell D, Evans SM, Nunes E, Akerele E, Donovan S, Vosburg SK. Pharmacotherapy for marijuana dependence: a double-blind, placebo-controlled pilot study of divalproex sodium. *Am J Addict*. 2004;13(1):21–32.
 129. Levy MH. Pharmacologic management of cancer pain. *Semin Oncol*. 1994;21(6):718–39.
 130. Lewis SA, Oswald I, Evans JI, Akindele MO, Tompsett SL. Heroin and human sleep. *Electroencephalogr Clin Neurophysiol*. 1970;28(4):374–81.
 131. Li X, Shorter D, Kosten TR. Buprenorphine in the treatment of opioid addiction: opportunities, challenges and strategies. *Expert Opin Pharmacother*. 2014;15(15):2263–75. doi:10.1517/14656566.2014.955469.
 132. Logan RW, Williams WP 3rd, McClung CA. Circadian rhythms and addiction: mechanistic insights and future directions. *Behav Neurosci*. 2014;128(3):387–412. doi:10.1037/a0036268.
 133. Maremmani I, Pani PP, Pacini M, Perugi G. Substance use and quality of life over 12 months among buprenorphine maintenance-treated and methadone maintenance-treated heroin-addicted patients. *J Subst Abuse Treat*. 2007;33(1):91–8. doi:10.1016/j.jsat.2006.11.009.
 134. Martin WR, Jasinski DR, Haertzen CA, Kay DC, Jones BE, Mansky PA, Carpenter RW. Methadone—a reevaluation. *Arch Gen Psychiatry*. 1973;28(2):286–95.
 135. Mason BJ, Crean R, Goodell V, Light JM, Quello S, Shadan F, et al. A proof-of-concept randomized controlled study of gabapentin: effects on cannabis use, withdrawal and executive function deficits in cannabis-dependent adults. *Neuropsychopharmacology*. 2012;37(7):1689–98. doi:10.1038/npp.2012.14.
 136. Mason BJ, Light JM, Williams LD, Drobos DJ. Proof-of-concept human laboratory study for protracted abstinence in alcohol dependence: effects of gabapentin. *Addict Biol*. 2009;14(1):73–83. doi:10.1111/j.1369-1600.2008.00133.x.
 137. Mason BJ, Quello S, Goodell V, Shadan F, Kyle M, Begovic A. Gabapentin treatment for alcohol dependence: a randomized clinical trial. *JAMA Intern Med*. 2014;174(1):70–7. doi:10.1001/jamainternmed.2013.11950.
 138. Matuskey D, Pittman B, Forselius E, Malison RT, Morgan PT. A multistudy analysis of the effects of early cocaine abstinence on

- sleep. *Drug Alcohol Depend.* 2011;115(1–2):62–6. doi:[10.1016/j.drugalcdep.2010.10.015](https://doi.org/10.1016/j.drugalcdep.2010.10.015).
139. Mednick SC, Christakis NA, Fowler JH. The spread of sleep loss influences drug use in adolescent social networks. *PLoS One.* 2010;5(3):e9775. doi:[10.1371/journal.pone.0009775](https://doi.org/10.1371/journal.pone.0009775).
 140. Mereu M, Bonci A, Newman AH, Tanda G. The neurobiology of modafinil as an enhancer of cognitive performance and a potential treatment for substance use disorders. *Psychopharmacology.* 2013;229(3):415–34. doi:[10.1007/s00213-013-3232-4](https://doi.org/10.1007/s00213-013-3232-4).
 141. Mogri M, Desai H, Webster L, Grant BJ, Mador MJ. Hypoxemia in patients on chronic opiate therapy with and without sleep apnea. *Sleep Breath.* 2009;13(1):49–57. doi:[10.1007/s11325-008-0208-4](https://doi.org/10.1007/s11325-008-0208-4).
 142. Monnelly EP, Ciraulo DA, Knapp C, LoCastro J, Sepulveda I. Quetiapine for treatment of alcohol dependence. *J Clin Psychopharmacol.* 2004;24(5):532–5.
 143. Monnelly EP, LoCastro JS, Gagnon D, Young M, Fiore LD. Quetiapine versus trazodone in reducing rehospitalization for alcohol dependence: a large data-base study. *J Addict Med.* 2008;2(3):128–34. doi:[10.1097/ADM.0b013e318165cb56](https://doi.org/10.1097/ADM.0b013e318165cb56).
 144. Montplaisir J, Lapierre O, Warnes H, Pelletier G. The treatment of the restless leg syndrome with or without periodic leg movements in sleep. *Sleep.* 1992;15(5):391–5.
 145. Morgan PT, Malison RT. Cocaine and sleep: early abstinence. *ScientificWorldJournal.* 2007;7:223–30. doi:[10.1100/tsw.2007.209](https://doi.org/10.1100/tsw.2007.209).
 146. Morgan PT, Malison RT. Pilot study of lorazepam and tiagabine effects on sleep, motor learning, and impulsivity in cocaine abstinence. *Am J Drug Alcohol Abuse.* 2008;34(6):692–702. doi:[10.1080/00952990802308221](https://doi.org/10.1080/00952990802308221).
 147. Morgan PT, Pace-Schott E, Pittman B, Stickgold R, Malison RT. Normalizing effects of modafinil on sleep in chronic cocaine users. *Am J Psychiatry.* 2010;167(3):331–40. doi:[10.1176/appi.ajp.2009.09050613](https://doi.org/10.1176/appi.ajp.2009.09050613).
 148. Morgan PT, Pace-Schott EF, Sahul ZH, Coric V, Stickgold R, Malison RT. Sleep, sleep-dependent procedural learning and vigilance in chronic cocaine users: evidence for occult insomnia. *Drug Alcohol Depend.* 2006;82(3):238–49. doi:[10.1016/j.drugalcdep.2005.09.014](https://doi.org/10.1016/j.drugalcdep.2005.09.014).
 149. Morgan PT, Pace-Schott EF, Sahul ZH, Coric V, Stickgold R, Malison RT. Sleep architecture, cocaine and visual learning. *Addiction.* 2008;103(8):1344–52. doi:[10.1111/j.1360-0443.2008.02233.x](https://doi.org/10.1111/j.1360-0443.2008.02233.x).
 150. Nicholson AN, Turner C, Stone BM, Robson PJ. Effect of delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. *J Clin Psychopharmacol.* 2004;24(3):305–13.
 151. Oyefeso A, Sedgwick P, Ghodse H. Subjective sleep-wake parameters in treatment-seeking opiate addicts. *Drug Alcohol Depend.* 1997;48(1):9–16.
 152. Pace-Schott EF, Morgan PT, Malison RT, Hart CL, Edgar C, Walker M, Stickgold R. Cocaine users differ from normals on cognitive tasks which show poorer performance during drug abstinence. *Am J Drug Alcohol Abuse.* 2008;34(1):109–21. doi:[10.1080/00952990701764821](https://doi.org/10.1080/00952990701764821).
 153. Pace-Schott EF, Stickgold R, Muzur A, Wigren PE, Ward AS, Hart CL, et al. Sleep quality deteriorates over a binge-abstinence cycle in chronic smoked cocaine users. *Psychopharmacology.* 2005;179(4):873–83. doi:[10.1007/s00213-004-2088-z](https://doi.org/10.1007/s00213-004-2088-z).
 154. Panagiotou I, Mystakidou K. Non-analgesic effects of opioids: opioids' effects on sleep (including sleep apnea). *Curr Pharm Des.* 2012;18(37):6025–33.
 155. Pasch KE, Latimer LA, Cance JD, Moe SG, Lytle LA. Longitudinal bi-directional relationships between sleep and youth substance use. *J Youth Adolesc.* 2012;41(9):1184–96. doi:[10.1007/s10964-012-9784-5](https://doi.org/10.1007/s10964-012-9784-5).
 156. Peles E, Schreiber S, Adelson M. Variables associated with perceived sleep disorders in methadone maintenance treatment (MMT) patients. *Drug Alcohol Depend.* 2006;82(2):103–10. doi:[10.1016/j.drugalcdep.2005.08.011](https://doi.org/10.1016/j.drugalcdep.2005.08.011).
 157. Peles E, Schreiber S, Adelson M. Documented poor sleep among methadone-maintained patients is associated with chronic pain and benzodiazepine abuse, but not with methadone dose. *Eur Neuropsychopharmacol.* 2009;19(8):581–8. doi:[10.1016/j.euroneuro.2009.04.001](https://doi.org/10.1016/j.euroneuro.2009.04.001).
 158. Peles E, Schreiber S, Hamburger RB, Adelson M. No change of sleep after 6 and 12 months of methadone maintenance treatment. *J Addict Med.* 2011;5(2):141–7. doi:[10.1097/ADM.0b013e3181e8b6c4](https://doi.org/10.1097/ADM.0b013e3181e8b6c4).
 159. Pickworth WB, Neidert GL, Kay DC. Morphinelike arousal by methadone during sleep. *Clin Pharmacol Ther.* 1981;30(6):796–804.
 160. Pivik RT, Zarcone V, Dement WC, Hollister LE. Delta-9-tetrahydrocannabinol and synhexl: effects on human sleep patterns. *Clin Pharmacol Ther.* 1972;13(3):426–35.
 161. Pjrek E, Frey R, Naderi-Heiden A, Strnad A, Kowarik A, Kasper S, Winkler D. Actigraphic measurements in opioid detoxification with methadone or buprenorphine. *J Clin Psychopharmacol.* 2012;32(1):75–82. doi:[10.1097/JCP.0b013e31823f91d1](https://doi.org/10.1097/JCP.0b013e31823f91d1).
 162. Post RM, Gillin JC, Wyatt RJ, Goodwin FK. The effect of orally administered cocaine on sleep of depressed patients. *Psychopharmacologia.* 1974;37(1):59–66.
 163. Prankoff K, Karacan I, Larson EA, Williams RL, Thornby JJ, Hirsch CJ. Effects of marijuana smoking on the sleep EEG. Preliminary studies. *JFMA.* 1973;60(3):28–31.
 164. Rawal N, Arner S, Gustafsson LL, Allvin R. Present state of extradural and intrathecal opioid analgesia in Sweden. A nationwide follow-up survey. *Br J Anaesth.* 1987;59(6):791–9.
 165. Ready LB, Loper KA, Nessly M, Wild L. Postoperative epidural morphine is safe on surgical wards. *Anesthesiology.* 1991;75(3):452–6.
 166. Roane BM, Taylor DJ. Adolescent insomnia as a risk factor for early adult depression and substance abuse. *Sleep.* 2008;31(10):1351–6.
 167. Robinson RW, Zwillich CW, Bixler EO, Cadioux RJ, Kales A, White DP. Effects of oral narcotics on sleep-disordered breathing in healthy adults. *Chest.* 1987;91(2):197–203.
 168. Roehrs T, Papineau K, Rosenthal L, Roth T. Ethanol as a hypnotic in insomniacs: self administration and effects on sleep and mood. *Neuropsychopharmacology.* 1999;20(3):279–86. doi:[10.1016/S0893-133X\(98\)00068-2](https://doi.org/10.1016/S0893-133X(98)00068-2).
 169. Roncero C, Grau-Lopez L, Diaz-Moran S, Miquel L, Martinez-Luna N, Casas M. Evaluation of sleep disorders in drug dependent inpatients. *Med Clin (Barc).* 2012;138(8):332–5. doi:[10.1016/j.medcli.2011.07.015](https://doi.org/10.1016/j.medcli.2011.07.015).
 170. Rosenthal M, Moore P, Groves E, Iwan T, Schlosser LG, Dziewanowska Z, Negro-Vilar A. Sleep improves when patients with chronic OA pain are managed with morning dosing of once a day extended-release morphine sulfate (AVINZA): findings from a pilot study. *J Opioid Manag.* 2007;3(3):145–54.
 171. Rundell OH, Williams HL, Lester BK. Sleep in alcoholic patients: longitudinal findings. *Adv Exp Med Biol.* 1977;85B:389–402.
 172. Satel SL, Price LH, Palumbo JM, McDougale CJ, Krystal JH, Gawin F, et al. Clinical phenomenology and neurobiology of cocaine abstinence: a prospective inpatient study. *Am J Psychiatry.* 1991;148(12):1712–6.
 173. Sattar SP, Bhatia SC, Petty F. Potential benefits of quetiapine in the treatment of substance dependence disorders. *J Psychiatry Neurosci.* 2004;29(6):452–7.
 174. Schiavi RC, Stimmel BB, Mandeli J, White D. Chronic alcoholism and male sexual function. *Am J Psychiatry.* 1995;152(7):1045–51.
 175. Schierenbeck T, Riemann D, Berger M, Hornyak M. Effect of illicit recreational drugs upon sleep: cocaine, ecstasy and marijuana. *Sleep Med Rev.* 2008;12(5):381–9. doi:[10.1016/j.smrv.2007.12.004](https://doi.org/10.1016/j.smrv.2007.12.004).
 176. Schmitz JM, Green CE, Stotts AL, Lindsay JA, Rathnayaka NS, Grabowski J, Moeller FG. A two-phased screening paradigm for evaluating candidate medications for cocaine cessation or relapse prevention: modafinil, levodopa-carbidopa, naltrexone. *Drug Alcohol Depend.* 2014;136:100–7. doi:[10.1016/j.drugalcdep.2013.12.015](https://doi.org/10.1016/j.drugalcdep.2013.12.015).
 177. Schmitz MM, Sepandj A, Pichler PM, Rudas S. Disrupted melatonin-secretion during alcohol withdrawal. *Prog Neuropsychopharmacol Biol Psychiatry.* 1996;20(6):983–95.
 178. Sharkey KM, Kurth ME, Anderson BJ, Corso RP, Millman RP, Stein MD. Obstructive sleep apnea is more common than central sleep apnea in methadone maintenance patients with subjective sleep complaints. *Drug Alcohol Depend.* 2010;108(1–2):77–83. doi:[10.1016/j.drugalcdep.2009.11.019](https://doi.org/10.1016/j.drugalcdep.2009.11.019).
 179. Sharkey KM, Kurth ME, Anderson BJ, Corso RP, Millman RP, Stein MD. Assessing sleep in opioid dependence: a comparison of subjective ratings, sleep diaries, and home polysomnography in methadone maintenance patients. *Drug Alcohol Depend.* 2011;113(2–3):245–8. doi:[10.1016/j.drugalcdep.2010.08.007](https://doi.org/10.1016/j.drugalcdep.2010.08.007).
 180. Shaw IR, Lavigne G, Mayer P, Choiniere M. Acute intravenous administration of morphine perturbs sleep architecture in healthy pain-free young adults: a preliminary study. *Sleep.* 2005;28(6):677–82.
 181. Sjogren P, Banning AM, Christensen CB, Pedersen O. Continuous reaction time after single dose, long-term oral and epidural opioid administration. *Eur J Anaesthesiol.* 1994;11(2):95–100.

182. Skoloda TE, Alterman AI, Gottheil E. Sleep quality reported by drinking and non-drinking alcoholics. In: Gottheil EL, editor. *Addiction research and treatment: converging trends*. Elmsford: Pergamon Press; 1979. p. 102–12.
183. Snyder S, Karacan I. Sleep patterns of sober chronic alcoholics. *Neuropsychobiology*. 1985;13(1–2):97–100.
184. Srisurapanont M, Jarusuraisin N. Amitriptyline vs. lorazepam in the treatment of opiate-withdrawal insomnia: a randomized double-blind study. *Acta Psychiatr Scand*. 1998;97(3):233–5.
185. Staedt J, Wassmuth F, Stoppe G, Hajak G, Rodenbeck A, Poser W, Ruther E. Effects of chronic treatment with methadone and naltrexone on sleep in addicts. *Eur Arch Psychiatry Clin Neurosci*. 1996;246(6):305–9.
186. Stein MD, Herman DS, Bishop S, Lessor JA, Weinstock M, Anthony J, Anderson BJ. Sleep disturbances among methadone maintained patients. *J Subst Abuse Treat*. 2004;26(3):175–80. doi:10.1016/S0740-5472(03)00191-0.
187. Stein MD, Kurth ME, Sharkey KM, Anderson BJ, Corso RP, Millman RP. Trazodone for sleep disturbance during methadone maintenance: a double-blind, placebo-controlled trial. *Drug Alcohol Depend*. 2012;120(1–3):65–73. doi:10.1016/j.drugalcdep.2011.06.026.
188. Stephens RS, Babor TF, Kadden R, Miller M, G Marijuana Treatment Project Research. The Marijuana Treatment Project: rationale, design and participant characteristics. *Addiction*. 2002;97(Suppl 1):109–24.
189. Stickgold R, Whidbee D, Schirmer B, Patel V, Hobson JA. Visual discrimination task improvement: a multi-step process occurring during sleep. *J Cogn Neurosci*. 2000;12(2):246–54.
190. Teichtahl H, Prodromidis A, Miller B, Cherry G, Kronborg I. Sleep-disordered breathing in stable methadone programme patients: a pilot study. *Addiction*. 2001;96(3):395–403. doi:10.1080/0965214002005374.
191. Teichtahl H, Wang D. Sleep-disordered breathing with chronic opioid use. *Expert Opin Drug Saf*. 2007;6(6):641–9. doi:10.1517/14740338.6.6.641.
192. Thompson PM, Gillin JC, Golshan S, Irwin M. Polygraphic sleep measures differentiate alcoholics and stimulant abusers during short-term abstinence. *Biol Psychiatry*. 1995;38(12):831–6. doi:10.1016/0006-3223(95)00070-4.
193. Trksak GH, Jensen JE, Plante DT, Penetar DM, Tartarini WL, Maywalt MA, et al. Effects of sleep deprivation on sleep homeostasis and restoration during methadone-maintenance: a [31P] MRS brain imaging study. *Drug Alcohol Depend*. 2010;106(2–3):79–91. doi:10.1016/j.drugalcdep.2009.07.022.
194. Vandrey R, Budney AJ, Kamon JL, Stanger C. Cannabis withdrawal in adolescent treatment seekers. *Drug Alcohol Depend*. 2005;78(2):205–10. doi:10.1016/j.drugalcdep.2004.11.001.
195. Vandrey R, Smith MT, McCann UD, Budney AJ, Curran EM. Sleep disturbance and the effects of extended-release zolpidem during cannabis withdrawal. *Drug Alcohol Depend*. 2011;117(1):38–44. doi:10.1016/j.drugalcdep.2011.01.003.
196. Vitiello M. Sleep, alcohol and alcohol abuse. *Addict Biol*. 1997;2:151–8.
197. Volavka J, Verebey K, Resnick R, Mule S. Methadone dose, plasma level, and cross-tolerance to heroin in man. *J Nerv Ment Dis*. 1978;166(2):104–9.
198. Vorspan F, Guillem E, Bloch V, Bellais L, Sicot R, Noble F, et al. Self-reported sleep disturbances during cannabis withdrawal in cannabis-dependent outpatients with and without opioid dependence. *Sleep Med*. 2010;11(5):499–500. doi:10.1016/j.sleep.2009.12.001.
199. Wagman AM, Allen RP. Effects of alcohol ingestion and abstinence on slow wave sleep of alcoholics. *Adv Exp Med Biol*. 1975;59:453–66.
200. Walker JM, Farney RJ. Are opioids associated with sleep apnea? A review of the evidence. *Curr Pain Headache Rep*. 2009;13(2):120–6.
201. Walker JM, Farney RJ, Rhondeau SM, Boyle KM, Valentine K, Cloward TV, Shilling KC. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. *J Clin Sleep Med*. 2007;3(5):455–61.
202. Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R. Practice with sleep makes perfect: sleep-dependent motor skill learning. *Neuron*. 2002;35(1):205–11.
203. Walsh JK, Randazzo AC, Stone K, Eisenstein R, Feren SD, Kajy S, et al. Tiagabine is associated with sustained attention during sleep restriction: evidence for the value of slow-wave sleep enhancement? *Sleep*. 2006;29(4):433–43.
204. Wang D, Teichtahl H. Opioids, sleep architecture and sleep-disordered breathing. *Sleep Med Rev*. 2007;11(1):35–46. doi:10.1016/j.smrv.2006.03.006.
205. Wang D, Teichtahl H, Drummer O, Goodman C, Cherry G, Cunningham D, Kronborg I. Central sleep apnea in stable methadone maintenance treatment patients. *Chest*. 2005;128(3):1348–56. doi:10.1378/chest.128.3.1348.
206. Wang D, Teichtahl H, Goodman C, Drummer O, Grunstein RR, Kronborg I. Subjective daytime sleepiness and daytime function in patients on stable methadone maintenance treatment: possible mechanisms. *J Clin Sleep Med*. 2008;4(6):557–62.
207. Watson R, Bakos L, Compton P, Gawin F. Cocaine use and withdrawal: the effect on sleep and mood. *Am J Drug Alcohol Abuse*. 1992;18(1):21–8.
208. Webster LR, Choi Y, Desai H, Webster L, Grant BJ. Sleep-disordered breathing and chronic opioid therapy. *Pain Med*. 2008;9(4):425–32. doi:10.1111/j.1526-4637.2007.00343.x.
209. Weddington WW, Brown BS, Haertzen CA, Cone EJ, Dax EM, Hering RI, Michaelson BS. Changes in mood, craving, and sleep during short-term abstinence reported by male cocaine addicts. A controlled, residential study. *Arch Gen Psychiatry*. 1990;47(9):861–8.
210. Weissman MM, Greenwald S, Nino-Murcia G, Dement WC. The morbidity of insomnia uncomplicated by psychiatric disorders. *Gen Hosp Psychiatry*. 1997;19(4):245–50.
211. Weller RA, Halikas JA. Change in effects from marijuana: a five- to six-year follow-up. *J Clin Psychiatry*. 1982;43(9):362–5.
212. Wetterberg L, Aperia B, Gorelick DA, Gwirtzman HE, McGuire MT, Serafetinides EA, Yuwiler A. Age, alcoholism and depression are associated with low levels of urinary melatonin. *J Psychiatry Neurosci*. 1992;17(5):215–24.
213. Williams HL, Rundell OH Jr. Altered sleep physiology in chronic alcoholics: reversal with abstinence. *Alcohol Clin Exp Res*. 1981;5(2):318–25.
214. Wong MM, Brower KJ, Fitzgerald HE, Zucker RA. Sleep problems in early childhood and early onset of alcohol and other drug use in adolescence. *Alcohol Clin Exp Res*. 2004;28(4):578–87.
215. Xiao L, Tang YL, Smith AK, Xiang YT, Sheng LX, Chi Y, et al. Nocturnal sleep architecture disturbances in early methadone treatment patients. *Psychiatry Res*. 2010;179(1):91–5. doi:10.1016/j.psychres.2009.02.003.
216. Young-McCaughan S, Miaskowski C. Definition of and mechanism for opioid-induced sedation. *Pain Manag Nurs*. 2001;2(3):84–97. doi:10.1053/jpmn.2001.25012.
217. Young-McCaughan S, Miaskowski C. Measurement of opioid-induced sedation. *Pain Manag Nurs*. 2001;2(4):132–49. doi:10.1053/jpmn.2001.25169.
218. Yue HJ, Guilleminault C. Opioid medication and sleep-disordered breathing. *Med Clin North Am*. 2010;94(3):435–46. doi:10.1016/j.mcna.2010.02.007.
219. Yules RB, Lippman ME, Freedman DX. Alcohol administration prior to sleep. The effect on EEG sleep stages. *Arch Gen Psychiatry*. 1967;16(1):94–7.
220. Zaks A, Fink M, Freedman AM. Duration of methadone induced cross-tolerance to heroin. *Br J Addict Alcohol Other Drugs*. 1971;66(3):205–8.
221. Zarcone V. Alcoholism and sleep. *Adv Biosci*. 1978;21:29–38.
222. Zehnder D, Hewison M. The renal function of 25-hydroxyvitamin D3-1 α -hydroxylase. *Mol Cell Endocrinol*. 1999;151(1–2):213–20.



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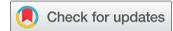
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Self-Medication for Sleep in College Students: Concurrent and Prospective Associations With Sleep and Alcohol Behavior

Patricia A. Goodhines^a, Les A. Gellis^a, Jueun Kim^a, Lisa M. Fucito^b, and Aesoon Park^a

^aDepartment of Psychology, Syracuse University, Syracuse, New York; ^bDepartment of Psychiatry, Yale School of Medicine, New Haven, Connecticut

ABSTRACT

Objective/Background: College students are at an increased risk for poor sleep and associated sleep problems. Emerging evidence suggests that a substantial subset of college students self-medicate with alcohol, marijuana, or over-the-counter medications to help sleep. The current study identified demographic, psychosocial, and sleep- and alcohol-related correlates of self-medication for sleep, and assessed its concurrent and prospective associations with insomnia symptoms, alcohol drinking, and negative drinking consequences. *Participants:* Undergraduate students ($N = 171$; mean age = 19 years [$SD = 1.35$], 32% male, 74% White) enrolled in a four-year university in the northeastern United States. *Methods:* Data were drawn from a short-term two-wave longitudinal study. Participants completed two online surveys, separated by an average interval of 68 days ($SD = 10.22$). *Results:* At Time 1, 25% of students reported using at least one substance (alcohol, marijuana, or over-the-counter medications) for sleep aid in the past two weeks. Male and older students were more likely to report using substances for sleep. Sleep aid use at Time 1 was concurrently associated with greater levels of alcohol frequency, negative drinking consequences, and insomnia symptoms. Further, sleep aid use at Time 1 was associated with an increase in negative drinking consequences from Time 1 to Time 2, but not with changes in alcohol frequency or insomnia symptoms. *Conclusions:* These findings indicate that substances are widely used among college students for sleep aid. Sleep aid use is associated with greater concurrent drinking and insomnia symptoms, and increases in negative drinking consequences over a short time period.

College students are at an increased risk for poor sleep and associated sleep problems. Approximately two thirds of college students do not get the recommended amount of sleep for their age group (i.e., 7–9 hr; Hirshkowitz et al., 2015; Lund, Reider, Whiting, & Prichard, 2010). Further, 12–23% of college students have endorsed clinically significant insomnia according to validated screening cutoffs (Gellis, Park, Stotsky, & Taylor, 2014; Gress-Smith et al., 2015). Poor sleep among college students has been concurrently associated with a plethora of problem behaviors, including increased alcohol consumption and physical illness (DeMartini & Fucito, 2014; Lund et al., 2010), fighting and risky sexual behaviors (Vail-Smith, Felts, & Becker, 2009), and motor vehicle accidents (Taylor & Bramoweth, 2010).

Emerging evidence suggests that a substantial subgroup of college students opt to self-medicate their sleep with substances such as alcohol, marijuana, and over-the-counter medications. In a large college student sample ($N = 1,125$), 10% of poor-quality sleepers endorsed using alcohol, and 33% endorsed using over-the-counter or prescription medications to help sleep (Lund et al., 2010). In another large study of college students ($N = 1,039$), 11% of all students endorsed the use of alcohol as

a sleep aid and 2% endorsed the use of over-the-counter medications, regardless of sleep quality (Taylor & Bramoweth, 2010). Despite the drastic increase in marijuana use among college students in recent years (Johnston, O'Malley, Bachman, Schulenberg, & Miech, 2015), however, no research has assessed marijuana use for sleep aid among college students. Given the limited number of extant studies, further research is needed to reconcile discrepancies in the prevalence of alcohol and over-the-counter medications for sleep aid and assess the likely prevalent trend of marijuana use for sleep aid among college students.

According to Brower's model of the reciprocal associations between insomnia and alcoholism (2003), self-medication for sleep is an integral part of a negative feedback loop of exacerbating insomnia and alcohol problems over time. This model maintains that insomnia increases alcohol use in an effort to self-medicate sleep; at the same time, however, alcohol use causes or worsens insomnia due to ethanol's toxicity on sleep-related brain systems. The troubling implication of this model is that the use of alcohol for sleep aid increases in response to worsening insomnia, thereby increasing the risk of worsening or relapsing alcohol problems over time. However, this model was developed for alcoholics and has not been applied to a college student sample. Thus, it remains unknown how insomnia and diverse alcohol behaviors synergistically influence each other over time among this group. Further, this feedback model has focused exclusively on alcohol and has not encompassed other substances commonly utilized for sleep aid such as over-the-counter medications or marijuana. The current study sought to apply this promising model to self-medication for sleep (alcohol, marijuana, and over-the-counter medications) among college students and examine its correlates and short-term insomnia- and alcohol-related outcomes.

Brower (2003) proposed several demographics (e.g., sex), depression and anxiety symptoms, sleep-related characteristics (e.g., sleep duration), and alcohol use patterns as correlates of co-occurring insomnia and alcoholism. However, it has yet to be examined whether the same set of factors along with other potentially relevant individual characteristics are associated with self-medication for sleep among college students. Such findings regarding demographic, sleep, and alcohol use characteristics associated with sleep aid use would be valuable in identifying at-risk students, potentially allowing for earlier intervention. Regarding demographics, a finding from the limited research of college students supports that male sex is indeed associated with alcohol sleep aid use (Taylor & Bramoweth, 2010). Given that full-time college students are homogeneous in terms of age (typically 18–25 years old; National Center for Education Statistics, 2016), and increases in alcohol frequency are not observed over time among college students (Nealis et al., 2017), age or legal drinking status may not be associated with substance use for sleep; however, these associations have yet to be tested empirically. Empirical evidence from insomnia and alcohol studies of college students suggests that negative mood and sleep- or alcohol-related characteristics may be associated with self-medication for sleep. Depression and anxiety symptoms have been associated with both insomnia (Gress-Smith et al., 2015), and alcohol or substance use and negative drinking consequences (Geisner, Mallett, & Kilmer, 2012; Kenney, Lac, LaBrie, Hummer, & Pham, 2013) among college students. Also, because sleep aid use is associated with poor sleep (Lund et al., 2010), it would be useful to characterize specific sleep-related characteristics that are associated with college students to self-medicate with substances. Presleep arousal (Nicassio, Mendlowitz, Fussell, & Petras, 1985), inconsistent sleep scheduling (Gellis et al., 2014), and evening circadian preference (Fernández-Mendoza et al., 2010) have been associated with poor sleep among college students and therefore worthy of exploring to establish their association with sleep aid use. Further, risky drinking patterns might predispose students to sleep aid use, as alcohol sleep aid has been concurrently associated with greater quantity of alcohol use (Lund et al., 2010).

Self-medication for sleep among college students is especially concerning, considering its potential role in the development of exacerbated alcohol and substance use and associated consequences over time. While alcohol, marijuana, and over-the-counter medications possess sedative qualities and are thus temporarily effective in initiating sleep onset (Chait & Perry, 1994; Rickels et al., 1983; Roehrs, Papineau, Rosenthal, & Roth, 1999), the use of sleep aids is shown to

negatively impact objective sleep measures. For example, alcohol use before bed typically results in more awakenings and restlessness during the second half of the night (Roehrs, Yoon, & Roth, 1991). Likewise, over-the-counter sleep aid use is associated with residual sedation during the following day and can also result in rebound insomnia, making it difficult to fall asleep naturally without sleep aid use (Katayose et al., 2012). Thus, self-medication for sleep may contribute to a dangerous feedback loop by which students hurt their sleep and continue to compensate with alcohol or substances, thereby increasing their risk of developing risky alcohol and substance use habits (Brower, 2003). This effect might be exacerbated by the fact that the desired effects of sleep aids reduce or extinguish over time (Bedi et al., 2010; Rundell, Lester, Griffiths, & William, 1972; Schweitzer, Muehlbach, & Walsh, 1994), likely leading sleep aid users to increase consumption to combat tolerance. For example, the desired effects of marijuana on sleep efficiency and satisfaction were found to last for only the first 8 days of intake, after which a higher dose would be required achieve similar effects (Bedi et al., 2010). However, research regarding sleep aid use among college students remains exclusively cross-sectional in nature, and therefore its prospective effects on subsequent insomnia symptoms, alcohol use, and alcohol problems over time are unknown.

Study aims and hypotheses

This study aimed to characterize prevalence of self-medication (alcohol, marijuana, and over-the-counter medication) for sleep among college students, identify its demographic, psychosocial, sleep, and alcohol-related correlates, and assess its short-term prospective associations with alcohol and sleep behaviors. Specifically, the current study examined differences between sleep aid users and nonusers in concurrent demographic, psychosocial, sleep-related, and alcohol-related characteristics. It was hypothesized that, compared to non-sleep aid users, sleep aid (i.e., alcohol, marijuana, and over-the-counter medication use for sleep) users would more likely be male, and report greater concurrent levels of depression or anxiety symptoms, poor sleep (i.e., shorter sleep duration, greater insomnia severity), sleep characteristics associated with poor sleep (i.e., greater sleep scheduling inconsistency, greater presleep arousal, and more evening circadian preference), alcohol frequency, and negative drinking consequences. Additionally, short-term prospective associations of sleep aid use with changes in insomnia severity, alcohol frequency, and negative drinking consequences were examined. It was hypothesized that sleep aid use would be associated with greater increases in insomnia severity, alcohol frequency, and negative drinking consequences over a short period of time.

Method

Participants and procedure

Data were drawn from a two-wave longitudinal study of 171 undergraduate students (mean age = 19 years [$SD = 1.35$, range = 18–28], 32% male) at a four-year university in the northeastern United States (Gellis et al., 2014; Park, Kim, Gellis, Zaso, & Maisto, 2014). Students were eligible to participate if they were 18 years of age or older and endorsed having had at least one alcoholic drink in the past 30 days. The sample consisted of 74% White, 12% Asian, 6% Black or African American, 6% multiracial, 1% American Indian or Alaska Native, and 1% missing on race. Participants were recruited from psychology classes and offered course credit incentive. Participants completed two online surveys, with an average interval of 68 days ($SD = 10.22$). Of the 171 participants at Time 1 (T1), 157 (92%) also participated at Time 2 (T2). A logistic regression including all T1 variables showed that attrition was predicted only by insomnia severity (OR = 1.24; 95% CI [1.04, 1.48]), indicating that students reporting greater insomnia severity at T1 were more likely to drop out from study.

Measures

Sleep aid use

Three investigator-developed items assessed past two-week frequencies of using alcohol, marijuana, and over-the-counter medications to help sleep at T1 and T2, such as, “How many days per week in the past 2 weeks have you taken alcohol to help you sleep at night?” In the absence of a standardized measure for sleep aid use, we utilized items from the Consensus Sleep Diary (Carney et al., 2012), modified wording appropriately for each substance, and adapted the response timeline for the past 2 weeks for consistency with the Insomnia Severity Index (Bastien, Vallieres, & Morin, 2001). Participants responded based on a 5-point scale (0 = 0 days, 1 = 1–2 days, 2 = 3–4 days, 3 = 5–6 days, 4 = 7 days). For main analyses, scores from these three items were combined to create a dichotomized variable representing any use of substances for sleep aid (0 = no sleep aid use, 1 = any sleep aid use). Test–retest reliability coefficient of this dichotomized sleep aid use measure from T1 to T2 was $r = .40$, $p < .001$, suggesting a moderate level of stability of sleep aid use over a 2-month period. The dichotomized score of each of these substance use items was utilized for ancillary analyses (see Data Analytic Strategies).

Demographics

Age, sex (0 = female, 1 = male), and legal drinking status (0 = under 21, 1 = 21 or older) were assessed at T1.

Depression or anxiety

The 4-item Patient Health Questionnaire was used at T1 and T2 to assess self-reported depression or anxiety symptoms in the past 2 weeks (Kroenke, Spitzer, Williams, & Löwe, 2009). Participants indicated how often during the past two weeks they experienced each symptom according to a 4-point scale (0 = not at all to 3 = nearly every day). A sum score (Cronbach's $\alpha = .79$) was used for analyses. This scale is a reliable and valid measure of depression and anxiety symptoms among college students (Khubchandani, Brey, Kotecki, Kleinfelder, & Anderson, 2016).

Sleep schedule

Four investigator-developed items assessed average sleep duration and the difference in sleep schedule between weekdays and weekends (i.e., social jet lag; Wittmann, Dinich, Mellow, & Roenneberg, 2006) in the past 2 weeks at T1 and T2. Participants identified times that they typically go to bed and wake up on weekdays and weekends (e.g., “During the past 2 weeks, what time have you usually gone to bed at night during the weekdays?”). Typical weekday and weekend sleep durations were calculated as time elapsed between bed times and wake times. Participants' weighted average sleep duration was calculated by averaging typical weekday sleep duration (multiplied by five days) and weekend sleep duration (multiplied by two days) over a seven-day period. Difference in weekday versus weekend bedtime was calculated as the absolute value after subtracting weekday bedtime from weekend bedtime. The use of comparable items and variable calculations are standard among college student samples (e.g., Singleton & Wolfson, 2009).

Morning–evening preference

The 19-item Morningness-Eveningness Questionnaire was used at T1 to identify participants' circadian preference (Horne & Ostberg, 1976), by assessing tiredness during the day, and preferred times to do diverse activities and to go to sleep. A sum score was utilized for the current analyses (range = 16–86; Cronbach's $\alpha = .72$), with a higher score indicating a morning (versus evening) circadian preference.

Insomnia severity

The 7-item Insomnia Severity Index was administered at T1 and T2 to assess a number of insomnia-related behaviors and their severity (Bastien et al., 2001). Participants indicated the extent to which

insomnia problems (e.g., difficulty falling asleep, waking up too early) impacted their following day based on a 5-point scale (0 = *None* to 4 = *Very severe*). The scale is a widely used assessment of insomnia severity (scores 0–7 = no clinically significant insomnia, 8–14 = subthreshold insomnia, 15–21 = moderate severity clinical insomnia, 22–28 = severe clinical insomnia; Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006; Smith & Wegener, 2003). A sum score (Cronbach's $\alpha = .86$) was used for analyses.

Pre-sleep arousal

The 16-item Pre-sleep Arousal Scale was administered at T1 and T2 to assess participants' typical state of arousal before sleep (Nicassio, Mendlowitz, Fussell, & Petras, 1985). Participants rated the severity of certain behaviors that may elicit pre-sleep arousal based on a 6-point scale (1 = *not at all* to 5 = *extremely*). A sum score (range = 16–18; Cronbach's $\alpha = .91$) was used for main analyses, with higher scores indicating a larger degree of difficulty in initiating sleep onset.

Alcohol frequency

One of the alcohol consumption items recommended by the National Institute on Alcohol Abuse and Alcoholism (2003) was used to measure alcohol frequency at T1 and T2. This item is widely used in college drinking studies and validated in college samples (e.g., Cranford, McCabe, & Boyd, 2006; Whiteman, Barry, Mroczek, & MacDermid Wadsworth, 2013; Zaso et al., 2016). The time frame was adapted from the past 12 months to the past 2 months to accommodate the two-month time lapse between T1 and T2 assessments, and response scales were adjusted accordingly (0 = *I did not drink any alcohol in the past 2 months*, 1 = *Once in the past 2 months*, 2 = *Once a month (twice in the past 2 months)*, 3 = *2 to 3 times a month (less than once a week)*, 4 = *Once or twice a week*, 5 = *3–4 times a week*, 6 = *5–6 times a week*, 7 = *Nearly every day*, 8 = *Every day*).

Negative drinking consequences

The 23-item Rutgers Alcohol Problem Index was administered at T1 and T2 to assess experiences of diverse negative consequences of alcohol consumption during the past two months (White & Labouvie, 1989). The time frame of this measure was modified from the past 12 months to accommodate the 2-month time frame of the current study. Participants indicated the frequency of experiencing alcohol-related problems (e.g., Had a bad time; Had a fight, argument, or bad feelings with a friend; Noticed a change in your personality; Neglected your responsibilities) based on a 7-point scale (0 = *Never in the past 2 months* to 6 = *Six times or more in the past 2 months*; Park et al., 2014). A sum score (Cronbach's $\alpha = .87$) was used for analyses. The sum score of the 23 items reflects the degree of experience of a range of diverse consequences (White & Labouvie, 1989), which has been demonstrated to map onto a single latent construct of negative drinking consequences (see Arterberry, Chen, Vergés, Bollen, & Martens, 2016; Cohn, Hagman, Graff, & Noel, 2011).

Data analytic strategies

Data analyses were computed using SPSS Version 23. Descriptive statistics and bivariate Pearson correlations were computed (see Table 1). Independent-sample *t*-tests and chi-square difference tests were conducted to compare sleep aid users to nonusers regarding all study variables at T1 and T2 (see Table 2). These group comparisons were for descriptive purposes to characterize the subgroup of college students who self-medicate for sleep versus those who do not without consideration of potential covariates (rather than identifying unique effects of sleep aid use over and above covariates, which were examined in the prospective regression analyses described below).

Using complete data of T1 and T2 ($n = 157$), regression analyses were utilized to examine short-term prospective relationships between T1 sleep aid use and T2 insomnia symptoms, alcohol frequency, and negative drinking consequences (see Table 3). The respective outcome variable at T1 was included as a covariate in each model (e.g., predicting Time 2 alcohol frequency after

**Table 1.** Descriptive statistics and bivariate correlations among study variables at Time 1 (T1) and Time 2 (T2).

Study variables	M (SD) or %	r																
		1	2	3	4	5	6	7	8	9	10	11	12	13	14			
(1) Sleep Aid Use at T1	25%	—																
(2) Male Sex (vs. Female)	32%	.16	—															
(3) Age (years) at T1	18.95 (1.35)	.23	.19	—														
(4) Legal Drinking Status at T1	12%	.19	.09	.78	—													
(5) Depression/anxiety at T1	3.65 (2.71)	.10	-.06	-.02	-.04	—												
(6) Average Sleep Duration (hours) at T1	7.97 (1.19)	-.10	.01	-.15	-.11	.16	—											
(7) Difference WE/WD bedtime (hours) at T1	2.14 (1.12)	-.03	.03	.05	.11	-.13	.10	—										
(8) Morning/Evening Preference at T1	46.81 (7.48)	-.09	-.01	.17	.23	-.08	-.05	.13	—									
(9) Insomnia Severity at T1	8.98 (5.48)	.20	-.13	.05	.11	.44	-.29	-.09	-.06	—								
(10) Presleep Arousal at T1	33.36 (10.90)	.18	-.16	-.12	-.07	.60	-.17	-.05	-.12	.66	—							
(11) Alcohol Frequency at T1	3.88 (0.98)	.21	.18	.04	.05	-.05	.05	.12	-.07	.03	.00	—						

(Continued)

Table 1. (Continued).

Study variables	M (SD) or %	<i>r</i>													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
(12) Negative Drinking Consequences at T1	11.42 (11.61)	.30	.06	-.05	.00	.35	-.13	.06	-.03	.34	.39	.34	—	—	—
(13) Insomnia Severity at T2	7.39 (5.30)	.20	-.03	.00	.03	.34	-.13	.03	-.12	.55	.49	.20	.28	—	—
(14) Alcohol Frequency at T2	3.71 (1.06)	.12	.06	-.02	-.02	-.11	.10	.12	-.12	-.03	-.04	.55	.16	.02	—
(15) Negative Drinking Consequences at T2	12.10 (15.61)	.30	.13	-.10	-.12	.24	-.10	-.01	-.20	.18	.30	.21	.40	.42	.18

Note. *N* = 171. WEAWD = weekend versus weekday. Significant group differences at $p < .05$ are highlighted in bold font.

Table 2. Means or percentages of study variables as a function of self-medication for sleep at Time 1.

Variable	Non-sleep aid users at Time 1 (75%; <i>n</i> = 128)	Sleep aid users at Time 1 (25%; <i>n</i> = 43)	Group comparison test statistics
Time 1 Variables (<i>N</i> = 171)			
Male Sex (vs. Female)	27%	44%	$\chi^2(1) = 4.23^*$
Age (years)	18.77 (1.03)	19.49 (1.96)	$t(169) = 2.29^*$
Legal Drinking Status	9%	23%	$\chi^2(1) = 6.42^*$
Depression or anxiety	3.50 (2.74)	4.09 (2.65)	$t(169) = 1.24$
Average Sleep Duration (hours)	8.05 (0.98)	7.76 (1.68)	$t(163) = -1.04$
Difference WE/WD bedtime (hours)	2.17 (1.08)	2.08 (1.22)	$t(163) = -0.43$
Morning–Evening Preference	47.18 (7.53)	45.70 (7.31)	$t(169) = -1.13$
Insomnia Severity	8.35 (5.04)	10.84 (6.31)	$t(169) = 2.62^{**}$
Pre-sleep Arousal	32.23 (9.99)	36.72 (12.79)	$t(169) = 2.37^*$
Alcohol Frequency	3.76 (0.95)	4.23 (1.00)	$t(169) = 2.79^{**}$
Negative Drinking Consequences	9.39 (9.74)	17.49 (14.45)	$t(169) = 3.42^{**}$
Time 2 Variables (<i>N</i> = 157)			
Sleep Aid Users	78% (<i>n</i> = 122)	22% (<i>n</i> = 35)	—
Insomnia Severity	6.82 (4.75)	9.40 (6.58)	$t(155) = 2.16^*$
Alcohol Frequency	3.65 (1.05)	3.94 (1.08)	$t(155) = 1.46$
Negative Drinking Consequences	9.63 (12.92)	20.7 (20.62)	$t(155) = 3.02^{**}$

Note. WE/WD = weekend versus weekday. Significant group differences at $p < .05$ are highlighted in bold font. $*p < .05$. $^{**}p < .01$.

Table 3 Regression analyses examining effect of sleep aid use at Time 1 on sleep and alcohol outcomes at Time 2.

	Time 2 outcomes		
	Insomnia severity	Alcohol frequency	Negative drinking consequences
Time 1 Sleep Aid Use	.11	-.01	1.63*
Time 1 Outcome	.48**	.54**	1.04**
Male Sex	.03	.08	1.57*
Time 1 Depression/anxiety	.13	-.09	1.07*
Time 1 Legal Drinking Status	-.04	-.04	0.56*

Note. *N* = 157. Sleep Aid Use = the use of any alcohol, marijuana, or over-the-counter medication for sleep aid in the past two weeks. Results of negative drinking consequences are based on a negative binomial regression, and incidence rate ratios are reported; results from all other variables are based on linear regressions, standardized coefficients are reported. Significant coefficients at $p < .05$ are highlighted in bold font.

$*p < .05$. $^{**}p < .001$.

controlling for Time 1 alcohol frequency). Sex, legal drinking status, and depression or anxiety symptoms were also included as covariates to control for their associations with insomnia and alcohol behaviors (Galambos, Vargas Lascano, Howard, & Maggs, 2013; S. R. Kenney, Jones, & Barnett, 2015; Lund et al., 2010). Linear regressions were used for normally distributed outcome variables of insomnia severity (skewness = 0.80; kurtosis = -0.16; range = 0–21) and alcohol frequency (skewness = -0.57; kurtosis = 1.35; range = 0–7; 0.6% did not drink any alcohol in the past 2 months at T2). Standardized regression coefficients were used for an effect-size measure of predictor variables. Negative binomial regressions were used for the over-dispersed outcome variable of negative drinking consequences (mean = 12.10; variance = 243.54; dispersion parameter = 0.96; skewness = 2.43; kurtosis = 6.35; range = 0–77; 9% reported no negative drinking consequences in the past 2 months at T2) as recommended by (Hilbe, 2011), and incidence rate ratios (IRR) were used for an effect-size measure of predictor variables.

Four sets of ancillary analyses were conducted. First, path analyses were conducted with all available data (*N* = 171) using missing data procedure of full-information maximum-likelihood estimation with robust standard errors (Graham, Cumsille, & Elek-Fisk, 2003) to assess the degree to which attrition at T2 (*n* = 14) affected results from regression analyses of complete data (*n* = 157). Second, to test for distinct patterns of specific substance used for sleep aid, separate regression analyses were conducted for each of alcohol, marijuana, and over-the-counter medication for sleep aid. Third, in order to rule

out polysubstance sleep aid use as a unique predictor of prospective sleep and alcohol use outcomes, regression analyses were repeated using number of sleep aids used (i.e., none, one, two, or all three) rather than dichotomized sleep aid use as the independent variable. Fourth, to test for the effect of sleep aid use initiation at T2 on changes in insomnia symptoms, alcohol frequency, and negative consequences over time, regression analyses were repeated using initiation of sleep aid use at T2 (instead of sleep aid use at T1) as the independent variable.

Results

Descriptive analyses

Descriptive statistics and bivariate Pearson correlation coefficients of study variables are reported in [Table 1](#). Participants reported 8 hr of sleep on average, subthreshold insomnia severity, and drinking alcohol 1–2 times per week at T1. At T1 and T2 assessments, 23–25% reported using any alcohol, marijuana, or over-the-counter medication for sleep aid in the past 2 weeks. Sleep aid use was significantly associated with alcohol frequency at Time 1 ($r = .21, p = .01$) but not at Time 2 ($r = .12, p = .15$), demonstrating a small to medium sized association at both time points. Regarding T1 alcohol variables, T1 sleep aid users reported drinking more frequently and experiencing more negative drinking consequences than nonusers.

Regarding specific substance used as sleep aid (data not shown in tables), 7–10% reported using alcohol, 14–15% reported using marijuana, and 14–16% reported using over-the-counter medications for sleep aid at T1 and T2 assessments. The average frequencies of all the three substances among users were 1–2 nights per week at T1 and T2. Of all participants, 19–21% reported using only one substance for sleep aid in the past two weeks, while 3–6% used two substances and 3–4% used all three. Among sleep aid users at T1 ($n = 43$), 63% also endorsed sleep aid use at T2. Out of nonsleep aid users at T1 ($n = 128$), 19% endorsed initiating sleep aid use at T2. Initiation of sleep aid use at T2 was not associated with insomnia symptoms at T1 ($r = -.06, p = .43$) or at T2 ($r = -.04, p = .63$) or any sleep-related characteristics at T1 (including morning–evening preference, $r = -.04, p = .58$; sleep duration, $r = .07, p = .42$).

Group comparisons between sleep aid users versus nonusers

[Table 2](#) presents results from independent-sample *t*-tests and chi-square tests to compare T1 sleep aid users and nonusers. Regarding demographics, T1 sleep aid users were more likely to be male, older, and at legal drinking age. Regarding T1 sleep variables, sleep aid users also reported higher insomnia severity and presleep arousal compared to nonusers, but no group differences were found in sleep duration, difference in weekday or weekend bedtime, or morning–evening preference. Regarding T1 alcohol variables, T1 sleep aid users reported drinking more frequently and experiencing more negative drinking consequences than nonusers.

Regarding T2 sleep and alcohol variables, T1 sleep aid users reported more negative drinking consequences and higher insomnia severity at T2 than nonusers. Groups did not differ in insomnia diurnal impact, presleep arousal, alcohol frequency, or heavy-drinking days at T2.

Prospective analyses

Results from regression analyses predicting insomnia symptoms, alcohol frequency, and negative drinking consequences at T2 from sleep aid use at T1 are presented in [Table 3](#). Sleep aid use at T1 was significantly and positively associated with T2 negative drinking consequences, even after accounting for T1 negative drinking consequences (i.e., changes in negative consequences over time) as well as sex, legal drinking age, and depression or anxiety symptoms. However, sleep aid use at T1 was not significantly associated with T2 insomnia severity or alcohol frequency after controlling for covariates.

Ancillary analyses

Path analyses of all available data using missing data procedure ($N = 171$) yielded the same patterns of significance as aforementioned linear and negative binomial regression analyses of complete data only ($n = 157$), suggesting that attrition at T2 ($n = 14$) was not likely to have affected overall findings.

Analyses of specific substance use for sleep aid showed that both alcohol ($IRR = 2.80, p = .006$) and marijuana ($IRR = 2.01, p = .004$) sleep aid use at T1 were significantly and positively associated with changes in negative drinking consequences, but not in insomnia symptoms or alcohol frequency. Time 1 over-the-counter medication use was not associated with any T2 outcomes at $p < .05$.

Analyses using number of sleep aids used (0 to 3) yielded results consistent with results from analyses using a dichotomized sleep aid use variable reported herein, indicating that the number of sleep aid use at T1 was positively associated with changes in negative drinking consequences, $IRR = 1.35, p = .01$, but not in insomnia symptoms and alcohol frequency at $p < .05$.

Analyses using the initiation of self-medication for sleep at T2 also yielded results consistent with results from analyses using T1 sleep aid use, indicating that the initiation of self-medication at Time 1 was significantly and positively associated with changes in negative drinking consequences ($IRR = 2.00, p = .003$), but not in insomnia symptoms or alcohol frequency at $p < .05$.

Discussion

This is the first prospective evaluation of sleep aid use and associated outcomes, broadening the knowledge of co-occurring sleep problems and substance use among college students. Of the current sample, 25% endorsed sleep aid use (i.e., alcohol, marijuana, or over-the-counter medication), suggesting that a substantial group of college students self-medicate to help sleep. Compared to nonusers, sleep aid users were more likely to be male, older, at legal drinking age, and reported higher levels of presleep arousal, insomnia severity, alcohol frequency, and negative drinking consequences. Sleep aid use was associated with an increase in negative drinking consequences, but not in alcohol frequency or negative drinking consequences over a short period of time. Further, initiation into self-medication for sleep was also associated with an increase in negative drinking consequences (but not in improvement in insomnia symptoms) over a two-month period. Collectively, these findings suggest that students self-medicating for sleep experience more adverse drinking consequences over time without the intended benefit of improved sleep.

Over-the-counter medications (14–16%) and marijuana (14–15%) were more popular choices of sleep aid than alcohol (7–10%), all of which were used 1–2 nights per week. A large study of college students (Taylor & Bramoweth, 2010) found prevalence and frequency of alcohol use for sleep aid relatively consistent with the current study, though over-the-counter medication use for sleep aid was notably less prevalent (2%) but more frequent (3–4 nights per week) than the current sample. Little is known about the frequency of over-the-counter medication use for sleep among college students, which makes it difficult to gauge potential reasons of this drastic difference in over-the-counter medication use for sleep (while a rate of alcohol use for sleep is comparable). Future multicampus studies of larger sample sizes should assess differences in diverse sleep aid preferences as a function of student demographics and campus characteristics.

Importantly, 7–9% of students endorsed utilizing multiple substances for sleep aid during the past two weeks. When consumed in combination, substances such as alcohol and marijuana have an additive effect on behavioral impairment (Chait & Perry, 1994). Further, polysubstance-using young adults are more likely to experience alcohol-related harm such as blackouts and acute memory loss (Hingson, Zha, Simons-Morton, & White, 2016). Therefore, these students potentially represent a group at increased risk of dangerous substance combinations. However, given the current study design, it cannot be determined whether students used multiple substances for sleep aid on a single evening. In order to investigate the prevalence and potential risk-associated polysubstance sleep aid

use, future studies should assess daily patterns of substance use, sleep aid selection, and negative consequences of substance use.

Several individual characteristics associated with this pattern of substance use (i.e., correlates) were identified. Sleep aid use was more common among men, consistent with extant findings (Taylor & Bramoweth, 2010). Sleep aid use was also more prevalent among older students and at legal drinking age. These unexpected results, which are not in line with findings in college drinking, may be due to the fact that students at legal drinking age have better access to alcohol than underage students, or that male and older students are more likely to be experienced alcohol or substance users, and therefore more readily opt to use alcohol or substances for sleep. This is consistent with our finding of a positive association between sleep aid use and concurrent alcohol frequency, suggesting that sleep aid users may use more substances for sleep mainly because they use more substances for a wider array of reasons in general. Extant literature has demonstrated that risky-drinking college students endorse higher levels of diverse drinking motives in general (e.g., coping and enhancement) compared to low-moderate risky-drinking peers (Littlefield, Vergés, Rosinski, Steinley, & Sher, 2013; Merrill et al., 2016). However, substance use for sleep motives has historically not been included in widely used alcohol or substance use motives assessments, which makes it difficult to assess unique effects of substance use for sleep over and above substance use for other reasons. Also, sleep aid users concurrently endorsed significantly more insomnia symptoms and presleep arousal compared to nonusers, but did not differ in average sleep duration, inconsistent sleep scheduling, or circadian preference. Students may use sleep aids to manage presleep arousal and insomnia symptoms (which may be improved by the sedative effects of sleep aids in a short term), but not sleep duration and inconsistent sleep scheduling (which are largely controlled by external factors such as class schedules and social events). Interestingly, sleep aid use was not concurrently associated with depression or anxiety symptoms, suggesting that sleep aid use is more driven by presleep factors and heavy and problematic substance use than mood-related problems. Overall, these findings suggest that some correlates of sleep aid use may differ from correlates of poor sleep (e.g., depression or anxiety, sleep duration, inconsistent sleep scheduling, or circadian preference) and of drinking behaviors (e.g., age or legal drinking age) among college students, albeit with some overlaps (e.g., male sex for drinking, and presleep arousal for insomnia). Further research is necessary to replicate these novel findings and investigate a more comprehensive set of correlates and proximal antecedents to sleep aid use.

The current findings also have significant implications for potential adverse consequences of sleep aid use over time. Sleep aid use was associated with increases in subsequent negative drinking consequences, but not with frequent drinking patterns. Despite the hypnotic effects of alcohol, alcohol use before bed negatively impacts sleep architecture, and tolerance to the hypnotic effects of alcohol develops rapidly (Roehrs et al., 1999), at which point associated functional impairments likely become exacerbated. Therefore, although students do not appear to increase the frequency of alcohol consumption over time, they may become more susceptible to the accompanying negative consequences (such as impaired school or work performance) due to repeated sleep aid use. Future research should examine the nuanced, day-to-day changes in the experiences of sleep, substance use, and associated consequences.

Contrary to a priori hypotheses, self-medication for sleep was not associated with changes in insomnia symptoms over this short period of time. Despite well-documented acute sleep disturbance following substance use for sleep aid (Katayose et al., 2012; Roehrs et al., 1991; Williams, MacLean, & Cairns, 1983), there appears to be no subjective detriment to sleep over a two-month period in college students. However, current findings do not rule out the possibility of long-term consequences of occasional or chronic sleep aid use among college students. Prospective longitudinal studies of a longer time lapse between assessments are needed to elucidate long-term sleep-related outcomes. Further, sleep aid users at T1 may have developed problematic sleep aid use habits prior to T1, and therefore the negative feedback loop outlined by Brower (2003) may have already begun, where self-medication for sleep leads to exacerbated insomnia symptoms and therefore increased self-medication over time. However, ancillary analysis results also provide preliminary evidence for the exacerbation of negative drinking consequences (but not of insomnia symptoms or alcohol frequency) from T1 to T2 as a result of initiation into sleep aid use at T2. Multiwave longitudinal studies with younger or inexperienced samples (e.g., adolescents) to track sleep aid users from the point of

initiation would help to resolve whether sleep aid use plays a unique role in the trajectory toward developing risky substance-use habits or dependence.

Limitations of the current study must be considered. Although this prospective design allows for a better assessment of temporal relationships than cross-sectional designs, the current study remains correlational in nature and thus causal inferences are speculative. Also, findings of the current study are based on subjective reports of sleep. Future investigators might consider the incorporation of objective sleep measures, such as actigraphy and polysomnography, which may be affected by sleep aid use. Also, the current analyses of self-medication for sleep did not account for potential confounding effects of using prescription medications for sleep (e.g., zolpidem, antidepressants, and benzodiazepines) that may be associated with sleep and alcohol or substance-use behaviors in complex ways. Another limitation is that items used to assess sleep aid use cannot isolate timing of use (i.e., initial sleep onset versus sleep reinitiation) or primary motivation for use (i.e., sleep aid versus other substance use reasons such as social, coping, and mood enhancement). These items also cannot determine a specific sleep problem for which individuals self-medicate (insomnia symptoms, other sleep-related disorders such as Delayed Sleep Phase Syndrome or obstructive sleep apnea, nightmares, etc.). Future studies should consider revising the phrasing of these items to explicitly assess timing of sleep aid use, as well as including additional items to investigate the primary motives of substance use before bed. Event-level investigations of motivation for substance use are necessary to isolate self-medication for sleep from alcohol and substance use for other purposes and to characterize the nuanced and dynamic associations among sleep, substance use, and associated consequences. Also, data were drawn from a predominantly White, first-year sample of students enrolled in a Northeastern private university. Because substance use and sleep patterns vary by diverse individual and school characteristics (Johnston et al., 2015; Lichstein, Durrence, Riedel, Taylor, & Bush, 2004), these sample characteristics should be considered in interpreting the findings of this study. Replication with larger and more representative samples is necessary for generalization of our findings, and further multicampus research may help to characterize how different school-level characteristics may be associated with distinct patterns of sleep aid use and its consequences over time. Additionally, students were eligible for participation only if they had consumed alcohol in the last 30 days; thus, the current findings might not be applicable to students who abstain from alcohol use (such as students utilizing exclusively marijuana or over-the-counter medications for sleep aid). In general college samples, approximately 80% of students endorse having used alcohol (Johnston et al., 2015). Further, mean levels of insomnia severity and alcohol use for sleep aid found in the current study were remarkably similar to prior studies of college students (Gress-Smith et al., 2015; Taylor & Bramoweth, 2010), suggesting that this sampling bias may not be substantial. Nonetheless, these sample characteristics should be considered when interpreting the current findings, and replication with more representative samples is necessary for generalization.

Despite the aforementioned limitations, the current findings present a significant step toward characterizing sleep aid use and its association with exacerbated negative drinking consequences over time. The current findings highlight the potential role of sleep aid use in the maintenance of co-occurring sleep problems and exacerbated substance problems among college students.

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References

- Arterberry, B. J., Chen, T., Vergés, A., Bollen, K. A., & Martens, M. P. (2016). How should alcohol problems be conceptualized? Causal indicators within the Rutgers Alcohol Problem Index. *Evaluation & the Health Professions*, 39(3), 356–378. doi:10.1177/0163278715616440
- Bastien, C. H., Vallieres, A., & Morin, C. M. (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Medicine*, 2(4), 297–307. doi:10.1016/S1389-9457(00)00065-4
- Bedi, G., Foltin, R. W., Gunderson, E. W., Rabkin, J., Hart, C. L., Comer, S. D., . . . Haney, M. (2010). Efficacy and tolerability of high-dose dronabinol maintenance in HIV-positive marijuana smokers: A controlled laboratory study. *Psychopharmacology*, 212(4), 675–686. doi:10.1007/s00213-010-1995-4
- Brower, K. J. (2003). Insomnia, alcoholism & relapse. *Sleep Medicine Reviews*, 7(6), 523–539. doi:10.1016/S1087-0792(03)90005-0
- Buysse, D. J., Ancoli-Israel, S., Edinger, J. D., Lichstein, K. L., & Morin, C. M. (2006). Recommendations for a standard research assessment of insomnia. *Sleep*, 29(9), 1155–1173. doi:10.1093/sleep/29.9.1155
- Carney, C. E., Buysse, D. J., Ancoli-Israel, S., Edinger, J. D., Krystal, A. D., Lichstein, K. L., & Morin, C. M. (2012). The Consensus Sleep Diary: Standardizing prospective sleep self-monitoring. *Sleep: Journal of Sleep and Sleep Disorders Research*, 35(2), 287–302. doi:10.5665/sleep.1642
- Chait, L. D., & Perry, J. L. (1994). Acute and residual effects of alcohol and marijuana, alone and in combination, on mood and performance. *Psychopharmacology*, 115(3), 340–349. doi:10.1007/BF02245075
- Cohn, A. M., Hagman, B. T., Graff, F. S., & Noel, N. E. (2011). Modeling the severity of drinking consequences in first-year college women: An item response theory analysis of the Rutgers Alcohol Problem Index. *Journal of Studies on Alcohol and Drugs*, 72(6), 981–990. doi:10.15288/jsad.2011.72.981
- Cranford, J. A., McCabe, S. E., & Boyd, C. J. (2006). A new measure of binge drinking: Prevalence and correlates in a probability sample of undergraduates. *Alcoholism: Clinical and Experimental Research*, 30(11), 1896–1905. doi:10.1111/j.1530-0277.2006.00234.x
- DeMartini, K. S., & Fucito, L. M. (2014). Variations in sleep characteristics and sleep-related impairment in at-risk college drinkers: A latent profile analysis. *Health Psychology*, 33(10), 1164–1173. doi:10.1037/hea0000115
- Fernández-Mendoza, J., Ilioudi, C., Montes, M. I., Olavarrieta-Bernardino, S., Aguirre-Berrocá, A., De La Cruz-Troca, J. J., & Vela-Bueno, A. (2010). Circadian preference, nighttime sleep and daytime functioning in young adulthood. *Sleep and Biological Rhythms*, 8(1), 52–62. doi:10.1111/j.1479-8425.2010.00430.x
- Galampos, N. L., Vargas Lascano, D. I., Howard, A. L., & Maggs, J. L. (2013). Who sleeps best? Longitudinal patterns and covariates of change in sleep quantity, quality, and timing across four university years. *Behavioral Sleep Medicine*, 11(1), 8–22. doi:10.1080/15402002.2011.596234
- Geisner, I. M., Mallett, K., & Kilmer, J. R. (2012). An examination of depressive symptoms and drinking patterns in first year college students. *Issues in Mental Health Nursing*, 33(5), 280–287. doi:10.3109/01612840.2011.653036
- Gellis, L. A., Park, A., Stotsky, M. T., & Taylor, D. J. (2014). Associations between sleep hygiene and insomnia severity in college students: Cross-sectional and prospective analyses. *Behavior Therapy*, 45(6), 806–816. doi:10.1016/j.beth.2014.05.002
- Graham, J. W., Cumsille, P. E., & Elek-Fisk, E. (2003). Methods for handling missing data. In J. A. Schinka & W. F. Velicer (Eds.), *Handbook of psychology: Research methods in psychology* (Vol. 2, pp. 87–114). Hoboken, NJ: Wiley
- Gress-Smith, J. L., Roubinov, D. S., Andreotti, C., Compas, B. E., & Luecken, L. J. (2015). Prevalence, severity and risk factors for depressive symptoms and insomnia in college undergraduates. *Stress and Health: Journal of the International Society for the Investigation of Stress*, 31(1), 63–70. doi:10.1002/smi.2509
- Hilbe, J. M. (2011). *Negative binomial regression* (2nd ed.). New York, NY: Cambridge University Press.
- Hingson, R., Zha, W., Simons-Morton, B., & White, A. (2016). Alcohol-induced blackouts as predictors of other drinking related harms among emerging young adults. *Alcoholism: Clinical and Experimental Research*, 40(4), 776–784. doi:10.1111/acer.13010
- Hirshkowitz, M., Whiton, K., Albert, S. M., Alessi, C., Bruni, O., DonCarlos, L., . . . Ware, J. C. (2015). National Sleep Foundation's updated sleep duration recommendations: Final report. *Sleep Health*, 1(4), 233–243. doi:10.1016/j.sleh.2015.10.004
- Horne, J. A., & Ostberg, O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International Journal of Chronobiology*, 4(2), 97–110.
- Johnston, L. D., O'Malley, P. M., Bachman, J. G., Schulenberg, J. E., & Miech, R. A. (2015). *Monitoring the Future national survey results on drug use, 1975–2014: Vol. 2. College students and adults ages 19–55* (pp. 416). Ann Arbor, MI: Institute for Social Research, The University of Michigan.
- Katayose, Y., Aritake, S., Kitamura, S., Enomoto, M., Hida, A., Takahashi, K., & Mishima, K. (2012). Carryover effect on next-day sleepiness and psychomotor performance of nighttime administered antihistaminic drugs: A randomized controlled trial. *Human Psychopharmacology*, 27(4), 428–436. doi:10.1002/hup.2244

- Kenney, S. R., Jones, R. N., & Barnett, N. P. (2015). Gender differences in the effect of depressive symptoms on prospective alcohol expectancies, coping motives, and alcohol outcomes in the first year of college. *Journal of Youth and Adolescence*, *44*(10), 1884–1897. doi:10.1007/s10964-015-0311-3
- Kenney, S. R., Lac, A., LaBrie, J. W., Hummer, J. F., & Pham, A. (2013). Mental health, sleep quality, drinking motives, and alcohol-related consequences: A path-analytic model. *Journal of Studies on Alcohol and Drugs*, *74*(6), 841–851. doi:10.15288/jsad.2013.74.841
- Khubchandani, J., Brey, R., Kotecki, J., Kleinfelder, J., & Anderson, J. (2016). The psychometric properties of PHQ-4 depression and anxiety screening scale among college students. *Archives of Psychiatric Nursing*, *30*, 457–462. doi:10.1016/j.apnu.2016.01.014
- Kroenke, K., Spitzer, R. L., Williams, J. B. W., & Löwe, B. (2009). An ultra-brief screening scale for anxiety and depression: The PHQ-4. *Psychosomatics: Journal of Consultation and Liaison Psychiatry*, *50*(6), 613–621.
- Lichstein, K. L., Durrence, H. H., Riedel, B. W., Taylor, D. J., & Bush, A. J. (2004). *Epidemiology of sleep: Age, gender, and ethnicity*. Mahwah, NJ: Lawrence Erlbaum.
- Littlefield, A. K., Vergés, A., Rosinski, J. M., Steinley, D., & Sher, K. J. (2013). Motivational typologies of drinkers: Do enhancement and coping drinkers form two distinct groups? *Addiction*, *108*(3), 497–503. doi:10.1111/j.1360-0443.2012.04090.x
- Lund, H. G., Reider, B. D., Whiting, A. B., & Prichard, J. R. (2010). Sleep patterns and predictors of disturbed sleep in a large population of college students. *Journal of Adolescent Health*, *46*(2), 124–132. doi:10.1016/j.jadohealth.2009.06.016
- Merrill, J. E., Treloar, H., Fernandez, A. C., Monnig, M. A., Jackson, K. M., & Barnett, N. P. (2016). Latent growth classes of alcohol-related blackouts over the first 2 years of college. *Psychology of Addictive Behaviors*, *30*(8), 827–837. doi:10.1037/adb0000214
- National Center for Education Statistics. (2016). *The condition of education, 2016*. Washington, DC: U.S. Department of Education.
- National Institute on Alcohol Abuse and Alcoholism. (2003). *Recommended alcohol questions*. Retrieved from <http://www.niaaa.nih.gov/>
- Nealis, L. J., Collins, J. L., Lee-Baggley, D. L., Sherry, S. B., & Stewart, S. H. (2017). One of these things is not like the others: Testing trajectories in drinking frequency, drinking quantity, and alcohol-related problems in undergraduate women. *Addictive Behaviors*, *66*, 66–69. doi:10.1016/j.addbeh.2016.11.010
- Nicassio, P. M., Mendlowitz, D. R., Fussell, J. J., & Petras, L. (1985). The phenomenology of the pre-sleep state: The development of the pre-sleep arousal scale. *Behaviour Research and Therapy*, *23*(3), 263–271. doi:10.1016/0005-7967(85)90004-X
- Park, A., Kim, J., Gellis, L. A., Zaso, M. J., & Maisto, S. A. (2014). Short-term prospective effects of impulsivity on binge drinking: Mediation by positive and negative drinking consequences. *Journal of American College Health*, *62*(8), 517–525. doi:10.1080/07448481.2014.929579
- Rickels, K., Morris, R. J., Newman, H., Rosenfeld, H., Schiller, H., & Weinstock, R. (1983). Diphenhydramine in insomniac family practice patients: A double-blind study. *The Journal of Clinical Pharmacology*, *23*(5–6), 234–242. doi:10.1002/jcph.1983.23.issue-5-6
- Roehrs, T., Papineau, K., Rosenthal, L., & Roth, T. (1999). Ethanol as a hypnotic in insomniacs: Self administration and effects on sleep and mood. *Neuropsychopharmacology*, *20*(3), 279–286. doi:10.1016/S0893-133X(98)00068-2
- Roehrs, T., Yoon, J., & Roth, T. (1991). Nocturnal and next-day effects of ethanol and basal level of sleepiness. *Human Psychopharmacology*, *6*(4), 307–311. doi:10.1002/hup.470060407
- Rundell, O. H., Lester, B. K., Griffiths, W. J., & William, H. L. (1972). Alcohol and sleep in young adults. *Psychopharmacologia*, *26*(3), 201–218. doi:10.1007/BF00422697
- Schweitzer, P. K., Muehlbach, M. J., & Walsh, J. K. (1994). Sleepiness and performance during three-day administration of cetirizine or diphenhydramine. *Journal of Allergy and Clinical Immunology*, *94*(4), 716–724. doi:10.1016/0091-6749(94)90179-1
- Singleton, Jr., R. A., & Wolfson, A. R. (2009). Alcohol consumption, sleep, and academic performance among college students. *Journal of Studies on Alcohol and Drugs*, *70*(3), 355–363. doi:10.15288/jsad.2009.70.355
- Smith, M. T., & Wegener, S. T. (2003). Measures of sleep: The Insomnia Severity Index, Medical Outcomes Study (MOS) Sleep Scale, Pittsburgh Sleep Diary (PSD), and Pittsburgh Sleep Quality Index (PSQI). *Arthritis & Rheumatism*, *49*(5S), S184–S196. doi:10.1002/art.11409
- Taylor, D. J., & Bramoweth, A. D. (2010). Patterns and consequences of inadequate sleep in college students: Substance use and motor vehicle accidents. *Journal of Adolescent Health*, *46*(6), 610–612. doi:10.1016/j.jadohealth.2009.12.010
- Vail-Smith, K., Felts, W. M., & Becker, C. (2009). Relationship between sleep quality and health risk behaviors in undergraduate college students. *College Student Journal*, *43*(3), 924–930.
- White, H. R., & Labouvie, E. W. (1989). Towards the assessment of adolescent problem drinking. *Journal of Studies on Alcohol*, *50*(1), 30–37. doi:10.15288/jsa.1989.50.30

- Whiteman, S. D., Barry, A. E., Mroczek, D. K., & MacDermid Wadsworth, S. (2013). The development and implications of peer emotional support for student service members/veterans and civilian college students. *Journal of Counseling Psychology, 60*(2), 265–278. doi:[10.1037/a0031650](https://doi.org/10.1037/a0031650)
- Williams, D. L., MacLean, A. W., & Cairns, J. (1983). Dose-response effects of ethanol on the sleep of young women. *Journal of Studies on Alcohol, 44*(3), 515–523. doi:[10.15288/jsa.1983.44.515](https://doi.org/10.15288/jsa.1983.44.515)
- Wittmann, M., Dinich, J., Merrow, M., & Roenneberg, T. (2006). Social jetlag: Misalignment of biological and social time. *Chronobiology International, 23*(1–2), 497–509. doi:[10.1080/07420520500545979](https://doi.org/10.1080/07420520500545979)
- Zaso, M. J., Park, A., Kim, J., Gellis, L. A., Kwon, H., & Maisto, S. A. (2016). The associations among prior drinking consequences, subjective evaluations, and subsequent alcohol outcomes. *Psychology of Addictive Behaviors, 30*(3), 367–376. doi:[10.1037/adb0000166](https://doi.org/10.1037/adb0000166)

Delta-9-tetrahydrocannabinol and synhexl: Effects on human sleep patterns

A series of experiments was conducted to determine the effects of orally administered 1-trans- Δ -9-tetrahydrocannabinol (THC) on both undisturbed and experimentally altered (by rapid eye movement [REM] deprivation) sleep patterns of young adult male volunteers. In the deprivation experiments, the effects of a semisynthetic Δ -6a-10-THC homologue, synhexl, were also studied. In the normative studies, 4 subjects received THC in doses ranging from 61 to 258 μ g per kilogram shortly before sleep onset, while in the deprivation experiments 2 subjects received either THC (244 μ g per kilogram and 259 μ g per kilogram) or synhexl (733 μ g per kilogram and 777 μ g per kilogram) the morning after the second of 2 consecutive nights of REM deprivation. In both normative and deprivation experiments, all-night sleep recordings were taken during base-line, drug, and postdrug conditions. The results of both types of experiments were consistent in demonstrating increments in Stage 4 sleep and decrements in REM sleep. In the normative experiments, reduction in Stage 1 and time awake after sleep onset were observed at the highest dose level. Interpretation of these results and their relation to the effects of other psychoactive compounds upon sleep patterns are discussed.

R. T. Pivik, Ph.D.,* V. Zarcone, M.D., W. C. Dement, M.D., Ph.D.,*** and L. E. Hollister, M.D.** Palo Alto, Calif.
Department of Psychiatry, Stanford University School of Medicine, and Veterans Administration Hospital

The many recent studies dealing with the behavioral and psychological effects of marijuana have served mainly to corroborate previous findings, prominent among which are reports of sedation and hallu-

cinatory-like behavior in lower animals^{12, 15, 31} and sleepiness, hallucinations, and fragmentation of thought in man.^{13, 14, 23} In one study, after oral ingestion of 1-trans- Δ -9-tetrahydrocannabinol (THC), subjects reported “. . . frequent bursts of disconnected dreams during brief periods of sleep between clinical trials.” These observations prompted the suggestion that THC might “enhance . . . dreaming sleep.”¹³ Empirical knowledge of the effects of THC on sleep is limited, however, to the observations

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*Supported by Biological Sciences Fellowship Training Grant MH 8304. Present address: Department of Psychiatry, Harvard Medical School, Boston, Mass.

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Table I. Schema of four normative experiments

Subject	Dosage level (mg.)	µg/Kg.	Consecutive recording days				
			B	D	PD	D	PD
Exp. I							
1	17	258	4	1	3	—	—
2	17	268	4	1	3	—	—
3	17	196	4	1	3	—	—
4	17	243	4	1	3	—	—
Exp. II							
3	13	150	4	1	1	—	—
Exp. III							
3	17	196	3	1	3	—	—
Exp. IV							
1	4.3	61	6	1	3	1	3
	8.6	123					
2	4.3	68	6	1	3	1	3
	6.8	135					

B = base-line, D = drug, PD = postdrug.

that it prolongs hexobarbital sleeping time in mice and rats^{9, 23} and, in rats, induces abnormal spiking discharges during sleep²² and reduces paradoxical sleep.²⁴ Only the latter studies used electrographic recording techniques and drew upon knowledge provided by recent studies which have established that mammalian sleep consists of the predictable cyclical alternation of two electrophysiologically different types of sleep: REM (rapid eye movement) and NREM (non-rapid eye movement).⁴ REM sleep is defined by the concomitance of a low-voltage, mixed-frequency electroencephalogram (EEG), electromyographic (EMG) atonia, and rapid eye movement. NREM sleep encompasses the remaining EEG variations occurring during sleep which extend from a low-voltage, mixed-frequency pattern to one of predominantly high-amplitude, slow waves. NREM sleep is associated with some degree of EMG activation and the general absence of eye movement. In man, reports of dreaming can be elicited from both kinds of sleep, but those from REM sleep are typically more numerous, more hallucinatory, and less conceptual than those from NREM sleep.⁷ Presumably, the suggestion that THC might enhance dreaming sleep refers to an increase in the amount of REM

sleep. We report here on a series of experiments conducted with the aim of gathering normative data on the effects of synthetic THC on human sleep patterns and examining the effects of this compound and a semisynthetic Δ -6a-10-THC homologue, synhexl, on sleep after REM deprivation.

Normative studies

Methods Four young adult male volunteers who had not used drugs for the preceding 2 month period served as subjects in the initial normative experiment. Three of the 4 were also the subjects in the remaining normative experiments. They abstained from drug use throughout. All subjects were directed to abstain from alcoholic beverages and daytime napping during the course of the experiments and not to eat during the 3 hours prior to reporting to the laboratory. All the normative studies, the designs of which are detailed in Table I, were double blind. Placebos were administered on all nondrug nights. Individual experiments were conducted with an intervening period of at least 2 months.

Marihuana extracts were prepared by alcoholic extraction of native marihuana on the basis of Δ -9-THC content determined by means of gas = liquid chromatography. Doses were based on THC con-

Table II. REM time expressed as per cent of total sleep time

Subject	Dose level (mg.)	Mean: B nights	Last B night	D night	First PD night	Mean: PD nights
1	17	21.5	26.9	21.8	23.2	26.2
2	17	19.6	20.6	15.5	22.5	20.6
3	17	21.3	19.2	27.2	19.9	23.9
4	17	23.9	30.0	21.4	27.5	26.5
3	17	21.6	19.2	16.2	19.9	22.9
3	13	25.9	25.3	24.5	22.6	22.6
1	4.3	24.9	24.5	18.4	20.7	23.2
2	4.3	20.4	22.9	27.8	26.8	24.9
1	8.6	24.9	24.4	19.4	24.7	26.3
2	8.6	20.4	22.9	20.1	34.3	26.6

B = base-line, D = drug, PD = postdrug.

tent; other cannabinoids, such as cannabidiol and cannabinol were present in undetermined amounts. A placebo which mimicked the extract in color and obnoxious taste was prepared by re-extracting with alcohol marijuana from which all cannabinoid had been removed by prior extraction. All materials were taken orally just prior to the beginning of sleep recordings. Subjects slept in separate sound-attenuated, darkened rooms and continuous recordings were taken from EEG, electrooculogram (EOG), and EMG electrodes placed in accordance with recommendations of the Rechtschaffen and Kales²⁸ standardized manual. These recordings were subsequently coded and scored blind according to the system set forth in the same manual.

All experiments were successfully concluded without the subjects experiencing any difficulty falling asleep or remaining so after initial sleep onset on any of the recording nights. That none of the subjects was able to differentiate drug nights from those on which placebos were given is noteworthy.

Results.

Effects on REM sleep. The mean percentages of total sleep time spent in REM sleep during base-line and postdrug recording periods, as well as the individual values for the last base-line night preceding the drug night and the first night subsequent to the latter, are shown in Table II. Values from the 3 nights were ranked

for each subject at every dose level, and in 7 of the 10 possible comparisons the drug night ranked lowest. The probability of obtaining such a series of relationships is 0.016 (binomial test). If a similar comparison is made substituting for the individual base-line and postdrug values their respective mean values, the drug nights still rank lowest most often (0.034, binomial).

Although there was almost always some reduction in REM time on drug nights, the decrement was relatively slight, i.e., the average reduction relative to the last base-line night was 2.1 percentage points for all comparisons and 4.38 percentage points for those 7 instances in which drug night ranked lowest.

To determine if the REM impairment was localized to a particular portion of the night, REM time occurring during the first and second halves of the last base-line night were compared (matched t test) with similar values from the drug night. The results indicated no significant difference between the first halves of the nights, but they did indicate a reduction ($p < 0.10$) in the amount of REM sleep during the second half of the drug night relative to that during the last base-line night. This effect was present for all subjects at the 17 mg. and 13 mg. dose levels ($p < 0.05$), but internal analyses revealed that only one subject consistently demonstrated the effect at the lower dose levels.

Effects similar to those reported above

Table III. Total sleep time (minutes)

Subject	Dose level (mg.)	Mean: B nights	Last B night	D night	First PD night	Mean: PD nights
1	17	400	401	412	392	383
2	17	404	384	407	441	418
3	17	450	452	452	471	469
4	17	444	456	450	464	456
3	17	434	435	448	420	444
3	13	447	451	477	454	—
1	4.3	375	362	405	423	414
2	4.3	414	409	415	437	422
1	8.6	375	400	425	409	386
2	8.6	414	440	418	426	417

B = base-line, D = drug, PD = postdrug.

might occur if total sleep time (TST) on the drug night was shortened relative to that on the preceding base-line night, thereby effectively reducing the amount of time available for REM sleep. Table III presents the mean total sleep times for all base-line and postdrug nights, as well as individual values for the last base-line night, the drug night, and the first post-drug night. Significantly more ($p < 0.01$) sleep was obtained on the drug night than on the last base-line night, whereas the differences between drug and first post-drug nights were not significant. A reduction of REM time concurrent with an increase in sleep time enhances the significance of the observed decrease.

Undisturbed sleep after a period of reduced REM sleep is generally characterized by increased REM relative to base-line levels.^{3, 5} A comparison between base-line and postdrug mean REM percentage values in these experiments revealed the presence of this effect on postdrug nights ($p < 0.05$). Internal analyses for the several dose levels indicated that the REM increment on postdrug nights tended to occur during the first half of the night—a tendency significant only at the 17 mg. dose level ($p < 0.05$). Although postdrug TST was greater than comparable base-line values ($p < 0.05$), the observation that the postdrug increase in REM time tended to occur in the initial portion of the night decreases the probability that the increase in REM time was due only to increased

TST. The probability is also challenged by the results of an analysis routinely used as an indicator of the presence of REM rebound—the latency from sleep onset to the first REM period. The reduction in latency values which typically occurs after REM deprivation has been interpreted as indicating an increased pressure for the expression of REM sleep.⁴ Postdrug latency values in these experiments were significantly less ($p < 0.05$) than were base-line values.

The data were examined for the presence of individual dose-dependent effects based on the effective microgram per kilogram dosage (see Table I). Aside from a general trend toward greater REM reduction with increased dosage, analyses based upon this variable were unremarkable. Individual variations in response to the drug were interesting. Subject 3 responded in an opposite manner to identical doses on two separate occasions, while Subject 1 had a more marked REM reduction at the lowest dosage level than at the highest.

Effects on NREM sleep. Mean percentages of NREM sleep stages on base-line and postdrug nights as well as individual drug night values are given in Table IV. Comparisons between last base-line or mean base-line and drug night values revealed no significant differences. Similar results were obtained from comparisons of base-line and postdrug NREM sleep stage values, with the single exception of Stage 1 sleep which demonstrated a sig-

Table IV. Pooled base-line, drug, and postdrug NREM sleep stage values (per cent of total sleep time) averaged across subjects within dose levels

Dose level (mg.)	All B nights	Last B night	D nights	PD nights
<i>Stage I</i>				
17	5.3	4.4	6.0	4.7
13	7.2	6.4	6.5	13.0
8.6	5.4	4.5	7.8	4.1
4.3	5.4	4.5	5.9	4.8
<i>Stage II</i>				
17	51.7	50.4	52.0	49.0
13	55.8	59.0	56.7	52.4
8.6	56.1	55.2	58.2	57.6
4.3	56.1	55.2	60.8	53.9
<i>Stage III</i>				
17	7.9	8.2	5.9	8.6
13	7.3	9.2	11.9	9.6
8.6	11.0	13.3	9.2	10.7
4.3	11.0	13.3	10.1	10.6
<i>Stage IV</i>				
17	12.1	12.9	16.8	15.3
13	3.5	0.0	0.4	2.6
8.6	4.3	4.4	5.2	3.7
4.3	4.3	4.4	0.1	4.1

B = base-line, D = drug, PD = postdrug. All values presented as means.

nificant postdrug reduction at the 17 mg. dose level ($p < 0.05$).

Since an analysis of the data in terms of halves of nights proved to be discriminative for REM sleep, similar analyses were conducted for NREM sleep stage data. The values on which these analyses were based were absolute amounts (minutes) of NREM sleep. Viewed in this way, the following effects were noted: (1) at the 17 mg. dose level only, significantly less ($p < 0.05$) Stage 2 sleep during the first half of the drug night relative to the first half of the last base-line night, and more ($p < 0.02$) of this sleep stage during the second half; (2) at all dose levels an increase ($p < 0.10$) in the amount of Stage 4 during the first half of the drug night relative to that time period on the last base-line night. This effect was most conspicuous at the 17 mg. level, at which

the amount of Stage 4 sleep obtained in the initial portion of the drug night exceeded comparable values for all subjects on all base-line nights by an average of 21 percentage points (47 per cent).

Half-night sleep stage comparisons between base-line and postdrug means of absolute values indicated postdrug reduction in Stage 1 sleep at the 17 mg. level which was greater during the first half of the night ($p < 0.05$) but which extended into the second portion of the night ($p < 0.10$). Although there were no other significant variations between base-line and postdrug NREM sleep stage mean values, slow-wave sleep (Stages 3 and 4 combined), which is normally concentrated during the first half of the night, was shifted in concentration to the second portion of the postdrug nights ($p < 0.02$).

Previous reports suggesting that THC might have sleep-inducing properties prompted the inspection of three variables commonly taken to indicate the presence of such an influence^{9, 14}: latency to sleep onset, time awake after sleep onset, and body movements during sleep of at least 15 second duration. The only significant change noted was a reduction at the 17 mg. dose level in the amount of time awake after sleep onset ($p = 0.016$); the average reduction on the drug night being 68 per cent of the base-line average (disregarding the first base-line night¹). It is noteworthy that postdrug values of this measure remain reduced.

Summary of normative studies. The results of these experiments indicate two main effects of THC on undisturbed sleep: increase in Stage 4 sleep and reduction in REM sleep. Both effects, including their sequential nature and time of onset with respect to drug ingestion, became more apparent when analyses were conducted on half- rather than whole-night sleep stage values. REM reduction, though slight, was of sufficient magnitude to permit the detection of "REM rebound" manifested by increased postdrug REM time and decreased latencies to the first REM

period. Other variations in sleep measures on drug and postdrug nights may be simply explained as displacements resulting from the two main effects. The decrease in Stage 2 on the first half of the drug night, for example, paralleled the increase in Stage 4, the increase in Stage 2 during the second half of the drug night was accompanied by a decrease in REM, and the postdrug redistribution of slow-wave sleep to the second half of the night was attended by an increased expression of REM sleep during the first half of the night.

A soporific effect of THC is suggested by the postdrug decrease in Stage 1 and the reduction in awake time after sleep onset on the drug night which was sustained in some measure through the postdrug nights. Since THC metabolites have been shown to be retained in plasma and excreted in urine for several days after administration,²⁰ such residual effects are possible. Similar variations in Stage 1 and the time spent after sleep onset are regularly observed during the course of adaptation to sleeping in the laboratory,¹ and such adaptation probably accounts in part for the effects observed here.

REM deprivation studies

A procedure to determine the potency of REM-reducing chemicals or manipulations is to introduce the REM-depriving agent during a period of REM rebound, i.e., immediately after REM deprivation. This postdeprivation period is characterized by REM sleep which is intensified both quantitatively and qualitatively relative to predeprivation levels.⁴⁻⁶ The procedure was used to test the extent of the REM-depriving capability of THC and to compare it with that produced by a semisynthetic Δ -6a-10-THC homologue, synhexl. The latter drug is similar to THC in its behavioral and physiological effects, including the production of dreamlike states, differing mainly in being less potent (potency ratio of synhexl to THC being about 3:1) and slower acting.¹⁴

Methods. Two young adult male volunteers (not participants in any of the normative experiments) underwent 3 separate REM deprivation procedures, each consisting of 2 nights of arousals. Each deprivation procedure was followed by 5 nights of undisturbed recovery sleep. Prior to the initial deprivation, 5 nights of baseline recordings were taken. Subjects were given either 20 mg. of THC or 60 mg. of synhexl orally (the effective microgram per kilogram doses being 244 and 259 for THC and 733 and 777 for synhexl) the morning after 2 of the 3 deprivation procedures. The third REM deprivation served as a control. Order of drugs was varied for the 2 subjects—one being control, synhexl, THC, the other, synhexl, THC, control. Electrode placements, scoring methods, and recording conditions, as well as all restrictions regarding daytime napping and ingestion of other drugs imposed during the earlier studies, were retained for these experiments. The REM deprivation procedure itself consisted of the artificial curtailment of each REM period by arousing the subject as near as possible to its onset as determined by electrographic criteria.

The amounts of REM sleep from each of the 3 recovery periods were compared with each other and with base-line data in a two-way analysis of variance with repeated measures.³³

Results. The data presented in Table V validate the REM deprivation manipulation and draw attention to the tremendous range of individual variation in immediate response to REM deprivation. The average reduction in percentage of total sleep time occupied by REM on deprivation nights relative to the average base-line value was 71.1 for Subject 5 and 91.9 for Subject 6. The degree of REM reduction was similar within subjects across the 3 different conditions. The between-subject difference in the extent of deprivation as well as the variation in the number of arousals necessary to implement the deprivation (overall deprivation days 3.2 times as many

Table V. Summary of data from control and treatment REM deprivation nights

Subject	Mean: B nights	Control*		THC		Synhexl	
		d ₁ †	d ₂	d ₁	d ₂	d ₁	d ₂
5							
% REM	23.8	5.6	7.5	4.9	8.6	6.2	8.4
Avg. % reduction‡		72.5		71.6		69.3	
No. of arousals		26	30	29	13	25	18
6							
% REM	26.1	2.5	1.9	1.6	2.7	2.0	2.0
Avg. % reduction		91.6		91.8		92.3	
No. of arousals		6	8	7	8	11	4

*Drugs (THC and synhexl) were administered on morning subsequent to d₂. No drug was administered following d₂ in control condition.

†d₁ = First deprivation night; d₂ = second deprivation night.

‡Avg. % reduction in REM time relative to the base-line average. Derived for each of the three deprivations using the following formula, where B \bar{x} = base-line mean:

$$\frac{2 B\bar{x} - (d_1 + d_2)}{2 B\bar{x}} \times 100.$$

Table VI. Analysis of variance of per cent REM time under base-line and REM deprivation recovery conditions

A				
Source	df	MS	F	
Between subjects				
Nights (A)	4	5.42	0.1035	
Subjects				
within groups	5	53.39		
Within subjects				
Conditions (B)	3	39.68	3.80*	
A × B	12	6.48	0.621	
Error	15	10.44		
B				
	Conditions			
	Base-line	Synhexl	THC	Control

Per cent REM:

Pooled averages 23.81† 24.34 25.68 28.27†

*p < 0.05.

†Control rebound significantly greater than base-line (p < 0.05, Tukey's (a) test). All other mean differences were nonsignificant.

arousals for Subject 5 as for Subject 6) reflect individual differences in response to the deprivation manipulation which are not subject to experimental control.

The results of the analysis of variance (Table VI) indicated the presence of a significant difference between the condition means, and Tukey's (a) test revealed that

the only significant difference (p < 0.05) among the means was that between control and base-line conditions. These results may be interpreted as demonstrating that: (1) under control condition these subjects responded to REM deprivation in the usual manner, i.e., with an increment in post-deprivation REM time which was significantly greater than base line, or (2) THC and synhexl, although not completely obviating the postdeprivation REM increase, diminished it substantially.

Since the normative studies indicated an increase in Stage 4 sleep subsequent to THC administration, an attempt was made to determine if a similar effect was obtained in the deprivation experiments. Fig. 1 illustrates changes in amounts of Stage 4 sleep across conditions as a function of treatment. These pooled data are based on 2 day totals (i.e., last 2 base-line days, the 2 deprivation days, and the first 2 recovery days) of Stage 4. The data corroborate the Stage 4 enhancing effect of THC and suggest a minimal capability in this respect for synhexl.

Discussion

The paucity of knowledge on the gastrointestinal rate of absorption of THC was a limitation which was relevant to the initial series of studies, since it precluded the possibility of specifying a priori the onset

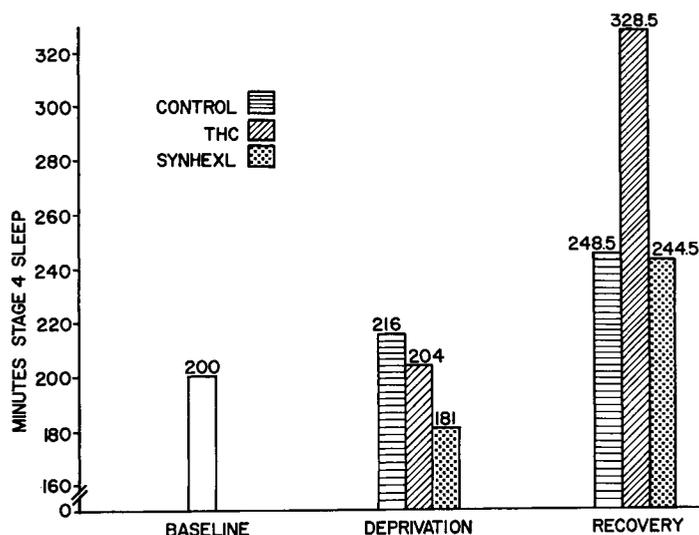


Fig. 1. Changes in amounts of Stage 4 sleep across conditions as a function of treatment. Pooled data are based on 2 day totals (i.e., last 2 base-line days, the 2 deprivation days, and the first 2 recovery days) of Stage 4.

of drug action. Although subjective effects of oral THC are reported to appear within 30 to 60 minutes,^{14, 16} the increment in Stage 4 sleep suggests that the onset of drug action occurred about 3 hours after ingestion. These observations indicate the insensitivity of the latency to sleep onset measure to any initial hypnotic properties of THC, since subjects were asleep well before the drug could have taken effect. The decrease in time spent awake after sleep onset and the increase in Stage 4 sleep, however, could be interpreted as indicating, respectively, less disturbed and "deeper" sleep,* thereby empirically supporting the attribution of sedative properties to THC.

Although both the normative and deprivation experiments indicate that THC reduces REM sleep, the degree of compensation was relatively less after the deprivation procedure. The simplest reconciliation of these data is one which regards the difference in terms of a delayed recovery phenomenon, i.e., a compensatory

process ultimately of normal proportions, but one whose full expression was in excess of the 5 day recovery period in these experiments. In the enforced deprivation condition, this process could have resulted from the convergence of several factors during the drug conditions which might have extended the deprivation effect, for example, the serial administration of REM-depriving agents (i.e., enforced arousals and REM-reducing drugs), drug action extending beyond the night of administration,²⁰ and a possible stress factor resulting from the daytime physiologic testing (including the taking of blood samples) which was not present during the control condition. Others have reported REM recovery periods extending over several weeks subsequent to the administration of psychoactive materials when such factors as listed above were not present.^{21, 26} Therefore, it is possible that our postdrug observations did not measure the full extent of the recovery process.

The notion that the hallucinations of both REM sleep and wakefulness are reflections of a single process is rooted in the phenomenological similarities of hallucinations from these 2 behavioral states^{8, 18} and has been enhanced by reports demonstrating

*For a discussion of the difficulties and nuances involved in defining depth of sleep see: Williams, H. L.: In Kety, S., Evarts, E., and Williams, H. L., editors: Sleep and altered states of consciousness, Baltimore, 1967, The Williams & Wilkins Company, pp. 277-287.

the hallucinogenic capability of several drugs derived from structurally dissimilar chemical groups (e.g., LSD, mescaline, phencyclidine, Ditran). If there is a mechanism common to all forms of hallucinogenesis, then REM sleep presents an unusual opportunity to pursue it. However, experimental evidence indicates that, with one exception—low doses of LSD enhance REM sleep in man,^{10, 25} while relatively high doses reduces REM sleep in the cat^{11, 32}—psychoactive drugs which induce walking hallucinations reduce REM sleep.^{2, 29} Furthermore, it has been demonstrated that the electrographic manifestations of walking hallucinations or hallucinatory-like behavior are more like those of slow-wave sleep^{12, 17, 34} than REM sleep.³⁰ It has long been known² that slow-wave sleep is capable of sustaining mental activity of a highly emotional nature, and the relative absence of recall of mentation from this kind of sleep²⁷ is suggestive of the diminished awareness which accompanies deeper hallucinogenic states during wakefulness.³⁴ It is possible, therefore that the naturally occurring state most comparable to that represented by induced waking hallucinations is slow-wave sleep rather than REM sleep. The results of both the normative and deprivation experiments, indicating an increase in Stage 4 sleep subsequent to ingestion of THC, are compatible with such a view.

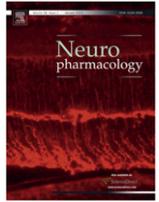
To place the results of these studies in proper perspective, an assessment of the potency of the doses used needs to be made. The effective dose levels in these experiments, which range from 61 μg per kilogram to 268 μg per kilogram, is below the level at which psychotomimetic effects are generally reported when THC is administered orally (300 to 480 μg per kilogram¹⁶). By these standards, our studies are based on low doses. This points up the sensitivity of sleep mechanisms to THC and synhexl and indicates that even subhallucinogenic doses exert relatively persistent effects.

Dr. Leo E. Hollister provided chemical compounds for these experiments. Δ -9-THC was obtained from the National Institute of Mental Health and was synthetic material provided by contract with Prof. R. Mechoulam, School of Pharmacy, Hebrew University, Jerusalem. The THC homologue, synhexl, was obtained from Dr. R. Gwinn, Abbott Laboratories, North Chicago, Ill.

References

1. Agnew, H. W., Webb, W. B., and Williams, R. L.: The first night effect: An EEG study of sleep, *Psychophysiology* **2**:263-266, 1966.
2. Broughton, R.: Sleep disorders: Disorders of arousal? *Science* **159**:1070-1078, 1968.
3. Dement, W.: The effect of dream deprivation, *Science* **131**:1705-1707, 1960.
4. Dement, W.: An essay on dreams: The role of physiology in understanding their nature, in Newcomb, T. M., editor: *New directions in psychology*, vol. II, New York, 1965, Holt, Rinehart & Winston, Inc., pp. 135-257.
5. Dement, W., Henry, P., Cohen, H., and Ferguson, J.: Studies on the effect of REM deprivation in humans and in animals, in Kety, S., Evarts, E., and Williams, H., editors: *Sleep and altered states of consciousness*, Baltimore, 1967, The Williams & Wilkins Company, pp. 456-468.
6. Dement, W., Zarcone, V., Ferguson, J., Cohen, H., Pivik, T., and Barchas, J.: Some parallel findings in schizophrenic patients and serotonin-depleted cats, in Sankar, S., editor: *Schizophrenia: Current concepts and research*, Hicksville, New York, 1969, PJD Publications, pp. 775-811.
7. Foulkes, D.: Dream reports from different stages of sleep, *J. Abnorm. Psychol.* **65**:14-25, 1962.
8. Freud, S.: *The interpretation of dreams*, New York, 1955, Basic Books, Inc.
9. Garriott, J. C., King, L. J., Forney, R. G., and Hughes, F. W.: Effects of some tetrahydrocannabinols on hexobarbital sleeping time and amphetamine induced hyperactivity in mice, *Life Sci.* **6**:2119-2128, 1967.
10. Green, W. J.: The effect of LSD on the sleep-dream cycle, *J. Nerv. Ment. Dis.* **140**:417-426, 1965.
11. Hobson, J. A.: The effect of LSD on the sleep cycle of the cat, *Electroencephalogr. Clin. Neurophysiol.* **17**:52-56, 1964.
12. Hocman, C. H., Perrin, R. G., and Kalant, H.: Electroencephalographic and behavioral alterations produced by Δ^1 tetrahydrocannabinol, *Science* **172**:968-970, 1971.

13. Hollister, L. E.: Marihuana in man: Three years later, *Science* **172**:21-29, 1971.
14. Hollister, L. E., Richards, R. K., and Gillespie, H. K.: Comparison of tetrahydrocannabinol and synhexl in man, *CLIN. PHARMACOL. THER.* **9**:783-791, 1968.
15. Holtzman, D., Lovell, R. A., Jaffe, J. H., and Freedman, D. X.: I- Δ^9 -Tetrahydrocannabinol: Neurochemical and behavioral effects in the mouse, *Science* **163**:1464-1467, 1969.
16. Isbell, H., Gorodetzky, C. W., Jasinski, D., Claussen, U., Spulak, F. V., and Korte, F.: Effects of (-) Δ^9 -trans-tetrahydrocannabinol in man, *Psychopharmacologia* **11**:184-188, 1967.
17. Itil, T., Fink, M., Neubauer, H., and Gershon, S.: Drug induced dissolution of cortical electrical activity and its correlation with psychopathological phenomena. Paper read at IV International Meeting of the Collegium International Neuropsychopharmacologicum, Birmingham, England, August, 1964.
18. Jackson, H. J.: Selected writings, Taylor, J., editor, vol. II, New York, 1958, Basic Books, Inc.
19. Kay, D. C., Eisenstein, R. B., and Jasinski, D. R.: Morphine effects on human REM state, waking state, and NREM sleep, *Psychopharmacologia* **14**:404-416, 1969.
20. Lemberger, L., Silberstein, R. B., Axelrod, J., and Kopin, I. J.: Marihuana: Studies on the disposition and metabolism of delta-9-tetrahydrocannabinol in man, *Science* **170**:1320-1322, 1970.
21. Lewis, S. A., Oswald, I., Evans, J. I., Akindele, M. O., and Tompsett, S. L.: Heroin and human sleep, *Electroencephalogr. Clin. Neurophysiol.* **28**: 374-381, 1970.
22. Masur, J., and Khazan, N.: Induction by cannabis sativa (marihuana) of rhythmic spike discharges overriding REM sleep electrocortigram in the rat, *Life Sci.* **9**:1275-1280, 1970.
23. Miras, C. J.: Some aspects of cannabis action, in Wolstenholme, G. E. W., and Knight, J., editors: *Hashish: Its chemistry and pharmacology*, Boston, 1965, Ciba Foundation Study Group, No. 21, Little, Brown & Company, pp. 37-53.
24. Moreton, J. E., and Davis, W. M.: Electroencephalographic study of effects of Δ^9 - and Δ^8 -tetrahydrocannabinol and cannabis extract on sleep in the rat, *Pharmacologist* **13**:246, 1971.
25. Muzio, J. N., Roffwarg, H. P., Kaufman, E.: Alterations in the nocturnal sleep cycle resulting from LSD, *Electroencephalogr. Clin. Neurophysiol.* **21**:313-324, 1966.
26. Oswald, I.: Human brain protein, drugs and dreams, *Nature* **223**:893-897, 1969.
27. Pivik, T., and Foulkes, D.: NREM mentation: Relation to personality orientation time, and time of night, *J. Consult. Clin. Psychol.* **32**: 144-151, 1968.
28. Rechtschaffen, A., and Kales, A., editors: A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects, Washington, D. C., 1968, United States Public Health Service Publication No. 204.
29. Rechtschaffen, A., and Maron, L.: The effect of amphetamine on the sleep cycle, *Electroencephalogr. Clin. Neurophysiol.* **16**:438-445, 1964.
30. Rechtschaffen, A., Shulsinger, F., and Mednick, S. A.: Schizophrenia and physiological indices of dreaming, *Arch. Gen. Psychiatry* **10**:83-93, 1964.
31. Scheckel, C. L., Boff, E., Dahlen, P., and Smart, T.: Behavioral effects in monkeys of racemates of two biologically active marijuana constituents, *Science* **160**:1467-1469, 1968.
32. Shimizu, A., and Himwich, H. E.: Effect of LSD on the sleep cycle of the developing kitten, *Dev. Psychobiol.* **1**:60-64, 1968.
33. Winer, B. J.: *Statistical principles in experimental design*, New York, 1962, McGraw-Hill Book Co., Inc.
34. Winters, W. D., and Wallach, M. B.: Drug induced states of CNS excitation: A theory of hallucinosis, in Efron, D. H., editor: *Psychotomimetic drugs*, New York, 1970, Raven Press, pp. 193-228.



Effect of cannabidiol on sleep disruption induced by the repeated combination tests consisting of open field and elevated plus-maze in rats

Yi-Tse Hsiao^a, Pei-Lu Yi^{a,b}, Chia-Ling Li^a, Fang-Chia Chang^{a,c,*}

^a Department of Veterinary Medicine, School of Veterinary Medicine, National Taiwan University, Taipei, Taiwan

^b Department of Sports, Health & Leisure, College of Sports Knowledge, Aletheia University, Matou Campus, Taiwan

^c Graduate Institute of Acupuncture Science, College of Chinese Medicine, China Medical University, Taichung, Taiwan

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ABSTRACT

Patients with post-traumatic stress disorder (PTSD) frequently complain of having sleep disturbances, such as insomnia and rapid eye movement (REM) sleep abnormality. Cannabidiol (CBD), a psychoinactive constituent of marijuana, reduces physiological non-REM (NREM) sleep and REM sleep in normal rats, in addition to generating its anxiolytic effect. However, the effects of CBD on anxiety-induced sleep disturbances remain unclear. Because anxiety progression is caused by persistent stress for a period of time, we employed the repeated combination tests (RCT) consisting of a 50-min open field (OF) and a subsequent 10-min elevated plus-maze (EPM) for four consecutive days to simulate the development of anxiety. Time spent in the centre arena of OF and during open arms of the EPM was substantially decreased in latter days of RCT, suggesting the habituation, which potentially lessens anxiety-mediated behavioural responses, was not observed in current tests. CBD microinjected into the central nucleus of amygdala (CeA) significantly enhanced time spent in centre arena of OF, increased time during the open arms and decreased frequency of entry to the enclosed arms of EPM, further confirming its anxiolytic effect. The decrease of NREM sleep during the first hour and the suppression of REM sleep during hours 4–10 after the RCT represent the similar clinical observations (e.g. insomnia and REM sleep interruption) in PTSD patients. CBD efficiently blocked anxiety-induced REM sleep suppression, but had little effect on the alteration of NREM sleep. Conclusively, CBD may block anxiety-induced REM sleep alteration via its anxiolytic effect, rather than via sleep regulation *per se*.

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1. Introduction

Anxiety disorders are the most common psychiatric disorders associated with sleep disruptions. In fact, sleep disturbances are included in the diagnostic criteria in two categories of anxiety disorders: general anxiety disorder (GAD) and post-traumatic stress disorder (PTSD) (American Psychiatry Association, 1994). Patients with GAD frequently complain to have difficulties falling asleep,

difficulties staying asleep, restless sleep, and unrefreshing sleep (American Psychiatry Association, 1994; Anderson et al., 1984), and persistent symptoms of increased arousal, insomnia, nightmares and disrupted rapid eye movement (REM) sleep are common sleep disorders in patients with PTSD (American Psychiatry Association, 1994; Horowitz et al., 1980; Mellman et al., 2002; Mellman and Davis, 1985; Neylan et al., 1998). Although anxiousness and worries are usually the causes of sleep disturbances in anxiety patients, sleep-specific pathologies and the other factor, such as stress *per se*, may develop and exacerbate sleep disruptions. The causal connection between sleep problems and anxiety are difficult to determine in the clinical aspect, and therefore the employment of an animal model of anxiety to study this relationship becomes adequate. The open field (OF) has been widely used to assess the behavioural effects of anxiety in rodents (Hall, 1936). Confrontation of the novel environment provided by the OF produces conflicting motivations between fear and exploration (Prut and Belzung, 2003; Welker, 1957). More thigmotaxis and less locomotion activity indicate greater anxiety, whereas greater exploration and more ambulation

Abbreviations: cAMP, cyclic AMP; CBD, cannabidiol; CeA, central nucleus of amygdala; DMSO, dimethyl sulfoxide; EEG, electroencephalogram; EMG, electromyogram; EPM, elevated plus-maze; GAD, general anxiety disorder; 5-HT, 5-hydroxytryptamine; ICV, intracerebroventricular; NREM, non-rapid eye movement; OF, open field; PTSD, post-traumatic stress disorder; RCT, repeated combination test; REM, rapid eye movement; SD, sleep deprivation; SWA, slow wave activity; Δ^9 -THC, Δ^9 -tetrahydrocannabinol.

* Corresponding author. Department of Veterinary Medicine, School of Veterinary Medicine, National Taiwan University, No. 1, Sec. 4, Roosevelt Road, Taipei 106, Taiwan. Tel.: +886 2 3366 3883; fax: +886 2 2366 1475.

E-mail address: fchang@ntu.edu.tw (F.-C. Chang).

to the centre arena of the OF reflect less emotion (Choleris et al., 2001). The elevated plus-maze (EPM), which is another rodent model for anxiety and used as a screening test for putative anxiolytics, consists of two open and two enclosed arms elevated 60 cm from the floor. This model is based on rodent's aversion of height and openness (Pellow et al., 1985; Treit et al., 1993). Because the progression of anxiety may be caused by the persistence of stress for a long period of time, we would like to mimic this anxiety development by exposing the animals to repeated stressors. However, a habituation behaviour may occur after repeated exposure to the OF. This anxiety-like behaviour is greater expressed during initial exposure to the OF, and exploration behaviour is increased as exposure time in the OF increases or with repeated exposure to the OF, indicating the lessened anxiety (Ivinskis, 1970; Makino et al., 1991). In contrast, anxiety behaviours expressed in the EPM have demonstrated a lack of habituation of exploration in the open arms because of the innate aversiveness of openness and height (Graeff et al., 1998; Treit et al., 1993). We herein employed the repeated combination tests (RCT), consisting of a 50-min of OF and a subsequent 10-min of EPM, for four consecutive days to simulate the anxiety development and anxiety-induced sleep disruptions.

Δ^9 -tetrahydrocannabinol (Δ^9 -THC) and cannabidiol (CBD) are two major constituents of the *Cannabis sativa* (ElSohly, 2002; Mechoulam, 1970). Two cannabinoid receptors, CB₁ and CB₂, are coupled to the pertussis toxin-sensitive G-protein, G_{i/o}, which inhibits adenylate cyclase and subsequently reduces the conversion of ATP to cyclic AMP (cAMP) (Chevalleyre et al., 2006). Δ^9 -THC has a strong binding affinity for central CB₁ receptors and produces psychoactive properties, including the anxiogenic effect (Grotenhermen, 2006), whereas CBD exhibits a low binding affinity for CB₁ receptors and has a non-psychoactive property (Grotenhermen, 2006; Mechoulam et al., 2002). The pharmacological property of the anxiolytic effect of CBD has been demonstrated in both animal researches (Guimaraes et al., 1990; Mechoulam et al., 2002; Pickens, 1981) and human studies (Crippa et al., 2004; Fusar-Poli et al., 2010), and becomes significant for therapeutic purposes. CBD also possesses sleep modulation effects; intracerebroventricular (ICV) administration of CBD during the light period increases wakefulness and decreases REM sleep in rats (Murillo-Rodríguez et al., 2006). We previously demonstrated that microinjection of CBD into the central nucleus of amygdala (CeA) decreases NREM sleep with limited effects on REM sleep suppression in normal rats (Yi et al., 2008). However, effects of CBD on anxiety-induced sleep disturbances have not been elucidated yet. CeA plays a key role in emotional processing, anxiety-related physiological and behavioural responses (Graeff et al., 1998), and its related behavioural responses, i.e. sleep–wake activity (Sanford et al., 1995). Here we determined the sleep disturbances induced after exposure of rats to RCT. Both effects of CBD, microinjected into the CeA, on sleep disturbances and the anxiolytic were evaluated. Comparing to the effects of CBD on spontaneous sleep regulation, present results would further elucidate whether the action of CBD on anxiety-induced sleep disturbance is mediated by its sleep regulation *per se* or is the consequence of anxiolytic action.

2. Materials and methods

2.1. Substances

Stock solution of CBD (Tocris, Bristol, UK) was dissolved in 2% dimethyl sulfoxide (DMSO). These stock solutions were stored at -20°C until administration. The doses of CBD used in these experiments were 0.5 and 1.0 μg . The total volume for each injection was 1 μl .

2.2. Animals

Male Wistar rats (250–300 g; National Laboratory Animal Breeding and Research Center, Taiwan) were used in these experiments. These animals were

anesthetized (ketamine/xylazine; 87/13 mg/kg), and injected with an analgesic (morphine) and antibiotic (penicillin G benzathine). Rats were surgically implanted with three electroencephalogram (EEG) screw electrodes (on the right hemisphere of the frontal and parietal lobes and the left hemisphere of the occipital lobe) as previously described (Chang and Opp, 1998), two neck electromyogram (EMG) electrodes, a thermistor (model: Pt100; Enercrop, Toronto, Canada) and a microinjection guide cannulae (26 gauge, O.D. 0.46 mm, I.D. 0.24 mm) directed into the CeA (AP, -2.8 mm from bregma; ML, 4.2 mm; DV, 7.8 mm relative to bregma). The coordinates were adopted from the Paxinos and Watson rat atlas (Paxinos and Watson, 1998). Insulated leads from EEG and EMG electrodes and the thermistor were routed to a Teflon pedestal (Plastics One, Roanoke, VA, USA). The Teflon pedestal was then cemented to the skull with dental acrylic (Tempron, GC Co., Tokyo, Japan). The incision was treated topically with polysporin (polymixin B sulphate–bacitracin zinc) and the animals were allowed to recover for seven days prior to the initiation of experiments. The rats were housed separately in individual recording cages in the isolated room, in which the temperature was maintained at $23 \pm 1^{\circ}\text{C}$ and the light:dark rhythm was controlled in a 12:12 h cycle (40 Watt \times 4 tubes illumination). Food and water were available *ad libitum*. We made our best effort to minimize animal suffering and to reduce the number of animals used in current study. All procedures performed in this study were approved by the National Taiwan University Animal Care and Use Committee.

On the second postsurgical day, rats were connected to the recording apparatus (see later) via a flexible tether. The location of the microinjection cannula was confirmed by injecting 0.5% trypan blue dye at the end of experiment. The recording data could be included for the subsequent analyses only when the injection target has been confirmed inside the CeA in rats. Animals were habituated by daily handling and injections of PFS timed to coincide with scheduled experimental administrations.

2.3. Apparatus and recording

Signals from the EEG electrodes were fed into an amplifier (Colbourn Instruments, Lehigh Valley, PA; model V75-01). The EEG was amplified (factor of 5000) and analogue bandpass was filtered between 0.1 and 40 Hz (frequency response: ± 3 dB; filter frequency roll off: 12 dB/octave). The EMG signals were also fed into an amplifier (CyberAmp 380; Axon Instruments, Union City, CA). Gross body movements were detected by custom-made infrared-based motion detectors (Bioobserve GmbH, Germany), and the movement activity was converted to a voltage output which was digitized and integrated into 1-s bins. The values of brain temperature were also converted to a voltage output by an analogue signal isolation transmitter (model: YT-TT3-A4; Yuden Electric Co., Ltd., Taiwan). These conditioned signals (EEGs, EMGs, brain temperature and gross body movements) were subjected to analogue-to-digital conversion with 16-bit precision at a sampling rate of 128 Hz (NI PCI-6033E; National Instruments, Austin, TX). The digitized EEG waveform and integrated values for body movement and brain temperature were stored as binary computer files pending subsequent analyses.

Postacquisition determination of the vigilance state was done by the visual scoring of 12-s epochs using custom software (ICELUS, M. R. Opp) written in LabView for Windows (National Instruments). The animal's behaviour was classified as either NREM sleep, REM sleep or waking based on previously defined criteria (Chang and Opp, 1998). Briefly, NREM sleep is characterized by large-amplitude EEG slow waves, high power density values in the delta frequency band (0.5–4.0 Hz), a relax muscle tone from EMGs, lack of gross body movements, and declining brain temperature before and during entry. During REMS, the amplitude of the EEG is reduced, the predominant EEG power density occurs within the theta frequency (6.0–9.0 Hz), the EMGs exhibit muscle atonia with low EMG amplitudes, brain temperature increases rapidly at onset, and there are phasic body twitches. During waking, the rats are generally active and brain temperature gradually increases. There are protracted body movements with robust EMG amplitudes. The amplitude of the EEG is similar to that observed during REM sleep, but power density values in the delta frequency band are generally greater than those in theta frequency band.

2.4. Behavioural tests

The OF chamber is a transparent Plexiglas squared box (100 cm \times 100 cm \times 50 cm), elevated at a height of 60 cm from the floor. The total areas of the OF were divided into nine arenas, including 4 corner arenas (30 cm \times 30 cm), 4 peripheral arenas (40 cm \times 30 cm) and one centre arena (40 cm \times 40 cm). The behavioural activities and movement traces were recorded by a digital camera, and this video file was imported to and analyzed by the custom software of Ethovision[®] (Version XT; Noldus, Wageningen, Netherlands). The time duration spent in the centre arena of the OF was determined as the major index for anxiety, and more ambulation towards the centre arena of the OF reflected less anxiety. Rats were placed in the centre arena of the OF at the beginning of the light (rest) period and exposed to the OF for 50 min. Activities were analyzed every 5-min and were represented by two 25-min time blocks.

After the 50-min exposure to the OF, rats were then placed in the cross area of the four arms and faced towards an open arm. The EPM consisted of two

open (50 cm long × 10 cm wide) and two enclosed arms (50 cm long × 10 cm wide × 40 cm height), and was elevated 60 cm from the floor. The performance of the EPM lasted for 10 min, and the traces of movement and activities in the EPM were recorded by a digital camera and analyzed by Ethovision®. The parameters of the movement traces in the EPM were classified as the time spent in the open arms, the frequency of entry to the open arms and the frequency of entry to the enclosed arms. The repeated combination tests (RCT) refer to the tests consisting of a 50-min OF and a subsequent 10 min EPM performed from the beginning of the light period in four consecutive days. The RCT was performed under 40 Watt × 4 tubes illumination, without noise and changing of environmental cues.

2.5. Experimental procedures

A total of 28 Wistar rats were used and divided into four groups as depicted in Fig. 1. A 24-h undisturbed baseline sleep recording was acquired before initiating experiments in all groups. Rats in group 1 (DMSO group; *n* = 7) received PFS and 2% DMSO 20 min prior to the beginning of the light period on the 1st and 2nd experimental days, respectively, and the sleep–wake activities were acquired for 24 h beginning from the light onset. The RCT of a 50-min OF and a 10-min EPM were performed during the first hour of the light period on the following 3rd, 4th, 5th and 6th days, and 2% DMSO was also administered 20 min prior to the light onset in these four consecutive days. The sleep–wake activities were recorded from the

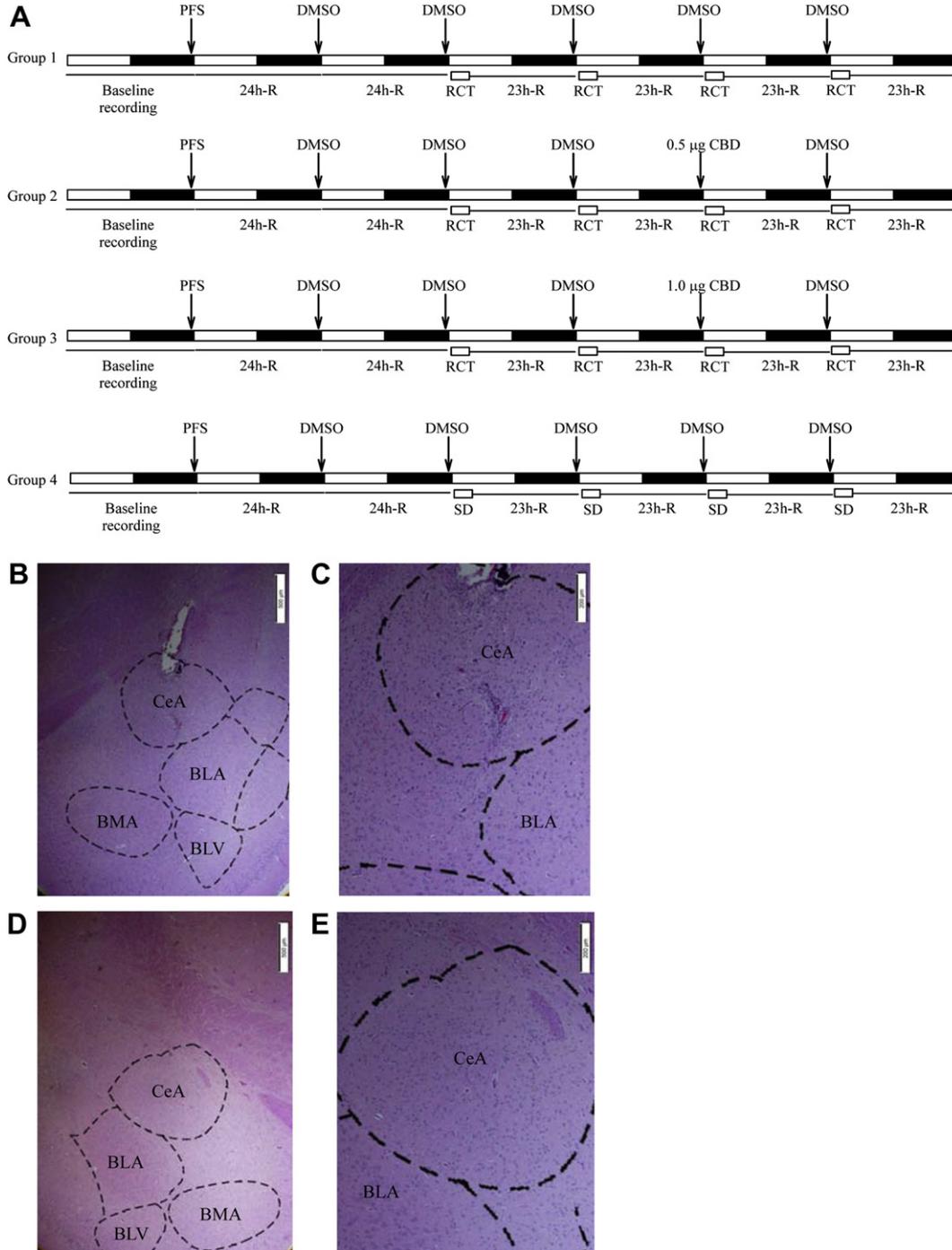


Fig. 1. A: The diagram for the experimental protocol. Close bar indicates the dark period and the open bar represents the light period of the 12:12 h light:dark cycle. Arrow depicts the timing of microinjection, “R” means recording, RCT represents the repeated combination test, and SD indicates sleep deprivation. B and C: the left CeA slides (with cannulae implantation); D and E: the right CeA slides (without implantation). CeA: central nucleus of amygdala; BLA: basolateral amygdala nucleus, anterior; BLV: basolateral amygdala nucleus, ventral; BMA: basomedial amygdala nucleus, anterior.

2nd-hour of the light period and lasted for 23 h. Rats in group 1 were used to determine the anxiogenic effect of the RCT and to evaluate the sleep disturbances. Rats in group 2 (low-dose CBD group; $n = 7$) received a protocol similar to those in group 1, except they were administered 0.5 μg CBD at the 5th days (the 3rd-day of RCT). Rats in group 3 (high-dose CBD group; $n = 7$) received a protocol similar to those in group 2, except they were administered 1.0 μg CBD at the 5th days (the 3rd-day of RCT). Groups 2 and 3 were used to determine the anxiolytic effect and the sleep effects of the CBD. Rats in groups 4 (sleep deprivation (SD) group; $n = 7$) were administered 2% DMSO 20 min prior to the beginning of the light period and were gently deprived of their total sleep for 1 h beginning from the light onset. The sleep-wake activities were recorded from the 2nd-hour of the light period and lasted for 23 h. Performing the RCT may have caused sleep deprivation during the first hour of the light period; however, results obtained from the rats in group 4 would eliminate the influence of sleep deprivation.

Additional 7 rats were used to verify the lesion of CeA after cannulae implantation and vehicle injection. Rats were implanted with a microinjection cannulae in the left hemisphere and received DMSO injection as those in group 1. Both left and right CeA regions were sliced, stained with haematoxylin and eosin, and the cell numbers were counted. Fig. 1B indicated the left CeA with cannulae implantation and Fig. 1D was obtained from the right CeA. Fig. 1C and E were the magnifications from Fig. 1B and D. The cell numbers counted from the left CeA and from the right CeA were 557.1 ± 29.9 and 554.4 ± 36.1 , respectively, suggesting there is no significantly physical damage to the CeA after implantation of microinjection cannulae and DMSO injection. Another 7 rats received the same protocol as those in group 1 and were used to clarify the level of anxiety by determining the urination and defecation.

2.6. Statistical analyses for experiment protocol

All values acquired from sleep-wake recording and the parameters of behaviour tests were presented as the mean \pm SEM for the indicated sample sizes. One-way repeated measures analyses of variance (ANOVA) for the duration of each vigilance state (NREM sleep, REM sleep, wakefulness), for sleep-architecture parameters, and for the parameters of behavioural tests were performed by comparing before, during and after manipulation within group and between groups, and across the two 12-h time blocks and specific time blocks as mentioned later in the result section. An α level of $p < 0.05$ was taken as indicating a statistically significant difference. If statistically significant differences were detected, a Tukey's multiple comparison was made to determine which values during experimental conditions deviated from those obtained from the control conditions. The correlation between the parameters obtained from the RCT and the number of days for exposing to the RCT was determined by the Spearman correlation coefficient.

3. Results

3.1. Behavioral measures of the repeated combination tests (RCT)

The values represented in Fig. 2 were the time differences for rats spending in the centre arena of the OF between second-day and first-day exposures of combination tests (Δ -day2), between third-day and first-day exposures (Δ -day3), and between fourth-day and first-day exposures (Δ -day4). The measures during the OF exposure were also divided into two 25-min blocks. The time for rats spending in the centre arenas of the OF during the total 50 min of exposure was gradually decreased as rats were repetitively exposed to the combination tests in the DMSO group; the Δ durations in the centre arena for Δ -day2, Δ -day3 and Δ -day4 were -0.7 ± 1.6 s, -3.3 ± 1.1 s and -3.5 ± 1.2 s, respectively (closed bars in Fig. 2C). Analysis for the durations in centre arena revealed it to be gradually and significantly decreasing when rats were repetitively exposed to the combination tests in four consecutive days ($F_{(3,207)} = 4.00$, $p < 0.01$). When comparing the values obtained from day-3 exposure to those acquired from day-1 exposure, a statistically significant difference was detected ($p < 0.05$; Fig. 2C). A similar result was observed when comparing the values between day-4 exposure and day-1 exposure ($p < 0.05$; Fig. 2C). The Spearman correlation coefficient (r) between the Δ duration in centre arena and the number of exposure to the OF was -0.19 ($p < 0.01$), indicating a negative correlation. Furthermore, the immobilization time was increased, and the total distance of movement and movement distance in the centre arena were consistently decreased following the repeated OF exposure

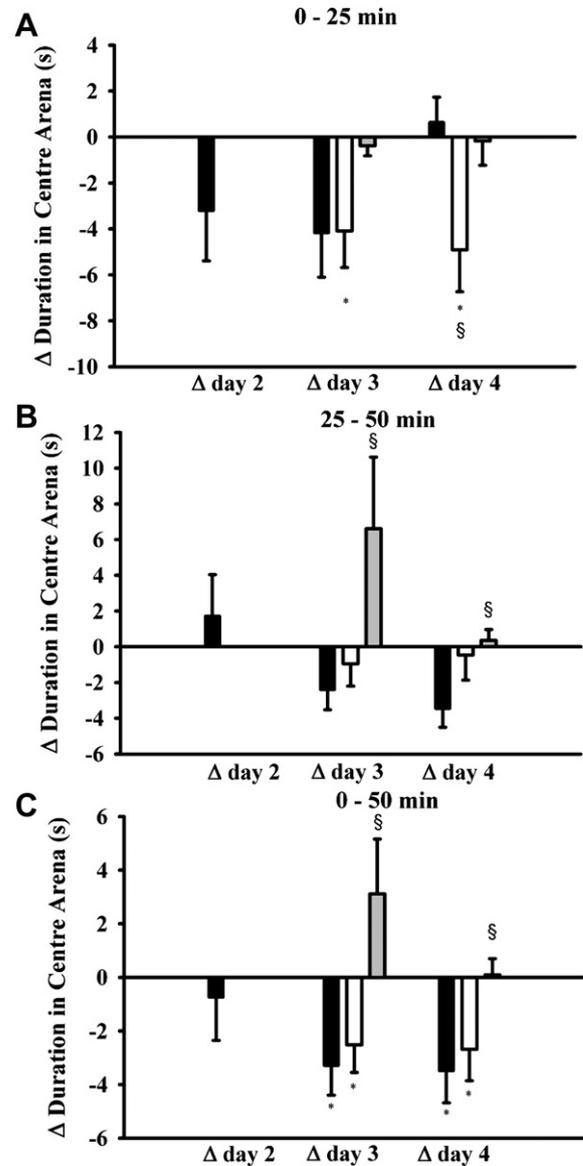


Fig. 2. The OF of RCT decreases the time spent during the centre arena and CBD increases rats' exploration in the central arena. The difference (Δ) of time duration spent in the centre arena of the OF is represented as mean \pm SEM in two 25-min blocks (A and B) and the whole 50-min block (C). Values in Δ -day2, Δ -day3 and Δ -day4 represent the differences determined after subtracting those acquired from day-1. Closed bars depict the values obtained from the DMSO group, open bars represent the values acquired from the low-dose (0.5 μg) CBD group, and grey bars demonstrate the values acquired from the high-dose (1.0 μg) CBD group. *represents a statistically significant difference when compared to the values obtained from day-1. § depicts a statistically significant difference when compared between the DMSO group and the CBD group on the same day.

(Table 1). This result suggests habituation learning as previous reports (Ivinskis, 1970; Makino et al., 1991) is not observed in the OF of the RCT and the anxiousness of rats also gradually increased as the stress exposure was repeated. We also found that the ambulation to the OF centre arena during the first 25-min time block was decreased during the day-2 and day-3 RCT exposures, whereas the anxiousness gradually increased during the second 25-min time block in the day-3 and day-4 exposures, which was indicated by the decrease of duration in the centre arena of the OF (closed bars in Fig. 2A and B).

The data (Δ -day2, Δ -day3 and Δ -day4) demonstrated in Fig. 3 were values of open arm durations, frequency of entry to the

Table 1

Parameters (immobilization time, total distance of movement, movement distance in the centre arena, and velocity in the centre arena) detected from the OF in three groups.

	Δ -day2	Δ -day3	Δ -day4
<i>Immobilization time (Sec)</i>			
Group 1 ^a	296.8 ± 95.9	235.0 ± 86.2	304.3 ± 68.6
Group 2	n.d. ^b	550.2 ± 255.4	486.7 ± 249.6
Group 3	n.d.	202.4 ± 97.4	170.8 ± 99.6
<i>Total distance of movement (cm)</i>			
Group 1	-1921.1 ± 665.6	-1572.0 ± 553.7	-2088.0 ± 465.2
Group 2	n.d.	-2217.3 ± 1065.2	-2070.6 ± 828.8
Group 3	n.d.	-1413.2 ± 545.3	-881.0 ± 774.5
<i>Movement distance in the centre arena (cm)</i>			
Group 1	-288.0 ± 99.1	-262.1 ± 124.3	-366.3 ± 104.0
Group 2	n.d.	-170.0 ± 354.3	-341.7 ± 270.7
Group 3	n.d.	18.6 ± 55.9	8.6 ± 47.3*
<i>Velocity in the centre arena (cm/s)</i>			
Group 1	3.8 ± 2.3	2.2 ± 1.8	3.5 ± 2.5
Group 2	n.d.	6.9 ± 1.8	1.6 ± 1.4
Group 3	n.d.	2.6 ± 8.6	-3.1 ± 2.2

Values are Means ± S.E.M. *denotes a statistically significant difference ($p < 0.05$) from values obtained from group 1.

^a Group 1: DMSO group; Group 2: 0.5 μ g CBD group; Group 3: 1.0 μ g CBD group.

^b n.d.: not determined.

open arms, frequency of entry to the enclosed arms and movement distance in the open arms in the EPM obtained from day-2, day-3 and day-4 exposures subtracting those acquired from day-1. Rats significantly spent less time in the open arms ($F_{(3,12)} = 4.3972$, $p < 0.05$; Δ -day2: $p < 0.05$; Δ -day4: $p < 0.05$) and decreased the frequencies of entry to the open arms of the EPM in day-2 and day-4 RCT exposures when compared to those obtained from day-1 in the DMSO group ($F_{(3,12)} = 5.9512$, $p < 0.05$; Δ -day2: $p < 0.05$; Δ -day4: $p < 0.05$; closed bars in Fig. 3A and B). The Spearman correlation coefficient (r) between Δ duration spent in the open arms and number of exposure to the EPM ($r = -0.45$, $p < 0.05$), and r between Δ frequency of entry to open arms and number of exposure to the EPM ($r = -0.48$, $p < 0.05$) revealed the negative correlation. The frequencies of entry to the enclosed arms of the EPM was sustainably decreased (Fig. 3C). The movement of distance in the open arms was also decreased following the repeated exposure of EPM, although it did not reach statistical significance (Fig. 3D). An example of trace analysis indicated the increase of avoidance of open arms when rats were repetitively exposed to the EPM (Fig. 3D, left panel).

Furthermore, the level of anxiety was additionally determined by the defecation and urination after exposing to RCT. Our results indicated that the volume of urine, number of defecation and weight of defecation were consistently increased following the RCT, indicating the level of anxiety did not diminished after the RCT, although these alterations did not reach statistical significance (Fig. 4).

3.2. Effects of CBD on repeated combination tests-induced behaviours

Microinjection of 1.0 μ g CBD directly into the CeA prior to the combination tests at the day-3 exposure statistically significantly enhanced the duration for rats exploring the centre arena of OF during the total of 50-min exposure (Δ -day3 = $+3.1 \pm 2.0$ s; grey bar in Fig. 2C) when compared to the values obtained from DMSO group rats at the day-3, which received 2% DMSO (Δ -day3 = -3.3 ± 1.1 s; $F_{(1,138)} = 7.55$, $p < 0.05$; closed bar in Fig. 2C). In addition, the Δ durations in the centre arena of the OF obtained from Δ -day4 significantly differ between the DMSO group and the high-dose CBD group, in which both groups received 2% DMSO

prior to the combination tests at day-4 exposure. The Δ duration in the centre arena obtained from Δ -day4 in the high-dose CBD group was $+0.1 \pm 0.6$ s, and the value acquired from Δ -day4 in the DMSO group was -3.5 ± 1.2 s ($F_{(1,138)} = 7.13$, $p < 0.01$; Fig. 2C). Further analyzing the alterations in the first and second 25-min time blocks revealed that CBD effect is significantly observed during the second 25-min time blocks (DMSO versus high-dose CBD groups at Δ -day3: $F_{(1,68)} = 4.69$, $p < 0.05$; DMSO versus high-dose CBD groups at Δ -day4: $F_{(1,68)} = 9.64$, $p < 0.01$; Fig. 2B). Administration of 0.5 μ g CBD exhibited no significant effect on OF-induced anxiousness as shown in Fig. 2. CBD did not change other parameters, including immobilization time, total distance of movement and velocity in the centre arena, obtained from repeated OF (Table 1). The OF-induced decrease of movement in the centre arena was suppressed by 1.0 μ g CBD, although it did not reach statistical significance. Notably, the OF-induced decreased movement in the centre arena was significantly suppressed at Δ -day4 in the high-dose CBD group ($p < 0.05$; Table 1).

Administration of CBD 1.0 μ g into the CeA reversed the decrease of the Δ durations in the open arms of EPM obtained from Δ -day3 and Δ -day4 in the DMSO group, although they did not reach statistical significance (Fig. 3A). The frequencies of entry to the enclosed arms of EPM were significantly decreased after receiving 1.0 μ g CBD at day-3, and 2% DMSO at day-4 of exposure in the high-dose CBD group when compared to those acquired at day-1 of exposure in the CBD group rats ($F_{(2,12)} = 14.61$, $p < 0.001$; Fig. 3C), and Tukey's multiple comparison indicated a statistically significant difference between values obtained at day-3 versus day-1 exposures ($p < 0.001$), and day-4 versus day-1 exposures ($p < 0.01$). Administration of CBD 1.0 μ g into the CeA suppressed the decrease of the Δ movement distance in the open arms of EPM obtained from Δ -day3 and Δ -day4 in the DMSO group, although they did not reach statistical significance (Fig. 3D). An example of trace analysis indicated that 1.0 μ g CBD blocked the avoidance of open arms when rats were repetitively exposed to the EPM in four consecutive days (Fig. 3D, right panel).

3.3. Sleep alterations induced after repetitive exposure to the combination tests

NREM sleep was not significantly altered during hours 2–12 after exposure to the RCT (Fig. 5B), except for the first hour after RCT. NREM sleep during the first hour after exposure to the RCT was significantly decreased in four consecutive days; the amounts of time spent in NREM sleep during hour-2 (the hour after RCT) were $50.1 \pm 6.7\%$ obtained after DMSO control, $13.0 \pm 5.7\%$ after day-1 exposure to tests, and $27.4 \pm 4.3\%$ after day-4 exposure to RCT in DMSO group ($F_{(2,12)} = 19.17$, $p < 0.001$; Fig. 5A), and Tukey's multiple comparison indicated a statistically significant difference when comparing the values after day-1 exposure versus control ($p < 0.001$), and day-4 exposure versus control ($p < 0.01$). Decreases of NREM sleep during the first hour after RCT were gradually decremented as the times of exposure to the RCT increased (Fig. 5A). Slow wave activities (SWAs) during NREM sleep was not significantly changed by the RCT; SWAs obtained from the control, day-1 exposure, day-2 exposure, day-3 exposure and day-4 exposure were $1069.1 \pm 2.9 \mu V^2/Hz$, $1079.2 \pm 4.2 \mu V^2/Hz$, $1073.5 \pm 2.8 \mu V^2/Hz$, $1075.5 \pm 3.4 \mu V^2/Hz$, and $1077.7 \pm 3.5 \mu V^2/Hz$, respectively. On the other hand, REM sleep was significantly reduced during hours 2–12 after exposure to the RCT (Fig. 5C and D). Analysis of sleep-architecture parameters across hours two to twelve revealed that the decrease in REM sleep after exposure to the RCT was primarily due to a decrease in REM sleep bout duration (Table 2). Further analysis of the first 5-h time block (hours 2–6) and second 6-h time block (hours 7–12) revealed that the RCT

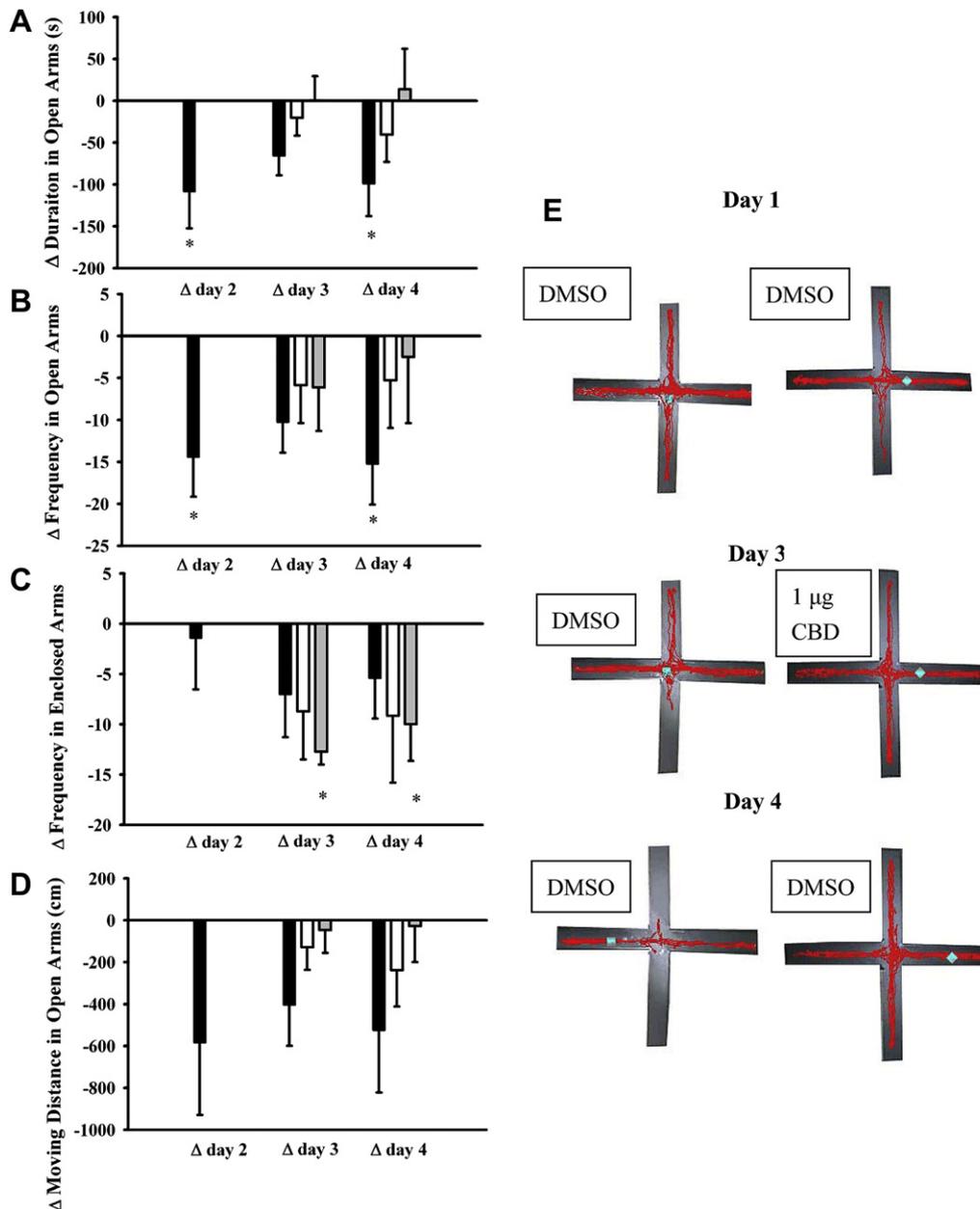


Fig. 3. The effects of CBD on the time rats spend in the open arms (A), the frequency of entering the open arms (B), the frequency of entering the enclosed arms (C), and movement distance in the open arms of the EPM (D). Values, represented as mean \pm SEM, in Δ -day2, Δ -day3 and Δ -day4 demonstrate the differences determined after subtracting those acquired from day-1. Closed bars depict the values obtained from the DMSO group, open bars represent the values acquired from the low-dose (0.5 μ g) CBD group, and grey bars demonstrate the values acquired from the high-dose (1.0 μ g) CBD group. *represents a statistically significant difference when compared to the values obtained from day-1. The red trace in panel E represents the track of rat's motion in the EPM. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

significantly decreased REM sleep during both time blocks (for hours 2–6: $F_{(4,136)} = 8.14$, $p < 0.001$; for hours 7–12: $F_{(4,164)} = 6.21$, $p < 0.001$; Fig. 5D), Tukey's multiple comparison indicated a statistically significant difference when comparing the values after day-1 exposure versus control (for hours 2–6: $p < 0.05$; for hours 7–12: $p < 0.05$), day-2 exposure versus control (for hours 2–6: $p < 0.01$; for hours 7–12: $p < 0.001$), day-3 exposure versus control (for hours 2–6: $p < 0.01$; for hours 7–12: $p < 0.001$), and day-4 exposure versus control (for hours 2–6: $p < 0.001$; for hours 7–12: $p < 0.001$). Further analysis of the alteration of REM sleep induced by the RCT has shown that the propensity of decrease in REM sleep was gradually augmented during the time block of hours

4–10 as the times of exposure to the RCT increased ($F_{(4,192)} = 7.02$, $p < 0.001$); the amounts of time spent in REM sleep obtained from the control, day-1 exposure, day-2 exposure, day-3 exposure and day-4 exposure were $21.1 \pm 1.1\%$, $18.8 \pm 1.0\%$ ($p > 0.05$: comparing with control), $16.5 \pm 1.2\%$ ($p < 0.01$: comparing with control), $15.6 \pm 1.2\%$ ($p < 0.001$: comparing with control), and $15.1 \pm 1.2\%$ ($p < 0.001$: comparing with control; $p < 0.05$: comparing with day-1 exposure), respectively.

Since performing the RCT during the first hour of the light period may deprive sleep, results obtained from the SD group were used to eliminate the influence of sleep deprivation. Our results indicated that NREM sleep was not significantly altered after 1-h

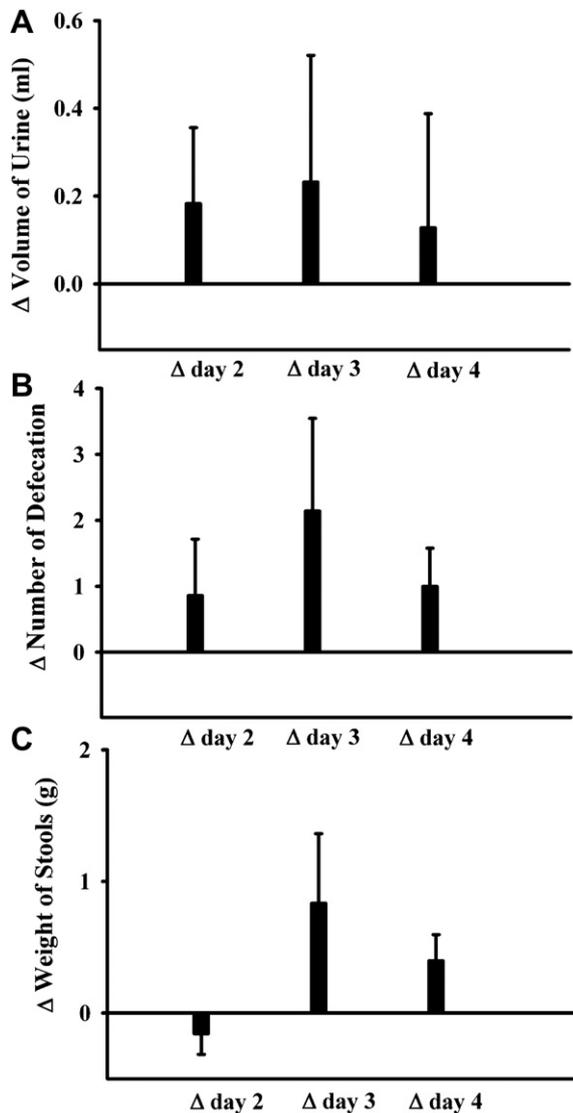


Fig. 4. The level of anxiety determined by urination and defecation after exposing to the RCT.

total SD, except for those during hour-1 after deprivation (Fig. 5E and F). The decrease of NREM sleep was gradually augmented as the times of SD increased; the percentages of time spent in NREM sleep obtained from the control, day-1 SD, and day-4 SD were $47.9 \pm 4.2\%$, $39.2 \pm 3.8\%$ and $24.5 \pm 8.6\%$ ($p < 0.01$: comparing with control; $p < 0.05$: comparing with day-1 SD; Fig. 5E). REM sleep was also not altered during hours 2–12 after SD, except the decrease of REM sleep was aware during the first few hours after SD (Fig. 5G and H). Significant rebounds of NREM sleep and REM sleep were noticed during the subsequent 12-h dark period as the times of SD increased (Fig. 5F and H).

3.4. CBD blocked RCT-induced suppression of REM sleep

Microinjection of 1.0 μg CBD directly into the CeA reversed the RCT-induced decrease of REM sleep during hours 4–10 when compared with the DMSO group (Fig. 6G). The amounts of time spent in REM sleep obtained from the control (2% DMSO), 2% DMSO + day-1 exposure, 1 μg CBD + day-3 exposure and 2% DMSO + day-4 exposure were $16.1 \pm 1.2\%$, $15.9 \pm 1.2\%$, $16.9 \pm 1.0\%$, and $19.0 \pm 1.1\%$ (no significance (n.s.); Fig. 6H), respectively.

However, 1.0 μg CBD had no effect on the initial suppression of NREM sleep and REM sleep after the RCT (Fig. 6E and F). Administration of 0.5 μg CBD also blocked RCT-induced decrease of REM sleep during hours 4–10 when compared with the DMSO group (Fig. 6C and D). Similarly, 0.5 μg CBD had no effect on the initial suppression of NREM sleep after the RCT (Fig. 6A).

4. Discussion

Persistent sleep disturbances, such as increased arousal, reduced sleep efficiency caused by increased wakefulness from sleep, insomnia, nightmares, disrupted REM sleep, and periodic limb movements, are highly prevalent in PTSD patients (American Psychiatry Association, 1994; Harvey and Bryant, 1998; Horowitz et al., 1980; Koren et al., 2002; Mellman et al., 2001, 2002; Mellman and Davis, 1985; Neylan et al., 1998). Growing evidence indicates that sleep disturbances are the core features of PTSD (rather than the secondary symptoms) and sleep disruption caused by the traumatic event may involve the pathological development of chronic PTSD (Germain et al., 2008). Although poor sleep efficiency, decrease of total sleep time, increase of sleep latency and increased number of awakenings are commonly found in the most of studies (Hefez et al., 1987; Lavie et al., 1979; Mikulincer et al., 1989), these findings are not observed in some other studies (Breslau et al., 2004; Ross et al., 1994). Disruption in REM sleep is also controversial; a shorter REM sleep time has been demonstrated (Hefez et al., 1987; Lavie et al., 1979; Mikulincer et al., 1989) but no change or a prolonged REM sleep was reported in others (Breslau et al., 2004; Fuller et al., 1994; Ross et al., 1994). The discrepant observations of sleep disruptions in PTSD patients may be due to the clinical variability, such as comorbidity, medication, age, sample size, and the time since the traumatic event (Fuller et al., 1994). Furthermore, whether disturbed sleep is the secondary symptom or the core feature of PTSD and the causal connection between sleep problems and anxiety are difficult to determine in the clinical aspect. Employment of a suitable animal model of PTSD becomes adequate for further investigation of the underlying mechanisms and for new drug development and screening. Exposure to psychological stress in humans is related to the increased incidence of PTSD (Brady and Sinha, 2005). Psychological stressors have a prominent effect on sleep alterations, particularly on REM sleep, although distinct stressors differ in REM alteration (Pawlyk et al., 2008). Pawlyk et al. summarize the effects of different stressors (including immobilization, footshock stress, and contextual fear conditioning) on sleep disruptions, and conclude that more intense stressors simulate anxiety and disrupt sleep (particularly REM sleep), although mild stressors might produce increases of REM sleep (Pawlyk et al., 2008). The OF is capable to induce anxiety in rodents and has been widely used to assess the behavioural effects of anxiety (Hall, 1936). The OF allows rodents to explore in a novel environment and produces conflicting motivations between fear and exploration with regards to the threatening environment. More thigmotaxis and less locomotion activity is thought to indicate greater anxiety, whereas greater exploration and more ambulation to the centre arena of the OF reflect less emotion (Choleris et al., 2001). EPM is another model to induce and assess anxiety based upon the confliction between exploration and aversion of height and openness (Pellow et al., 1985; Treit et al., 1993). Repetitive exposure to stress or exposure to a persistent stressor for a long period of time might participate in the development of anxiety. However, the OF exhibits the habituation behaviour after repetitive exposure to the OF or increased exposure time in the OF (Ivinskis, 1970; Makino et al., 1991). We employed RCT consisting of 50 min of OF and a subsequent 10-min of EPM for four consecutive days to simulate the development of

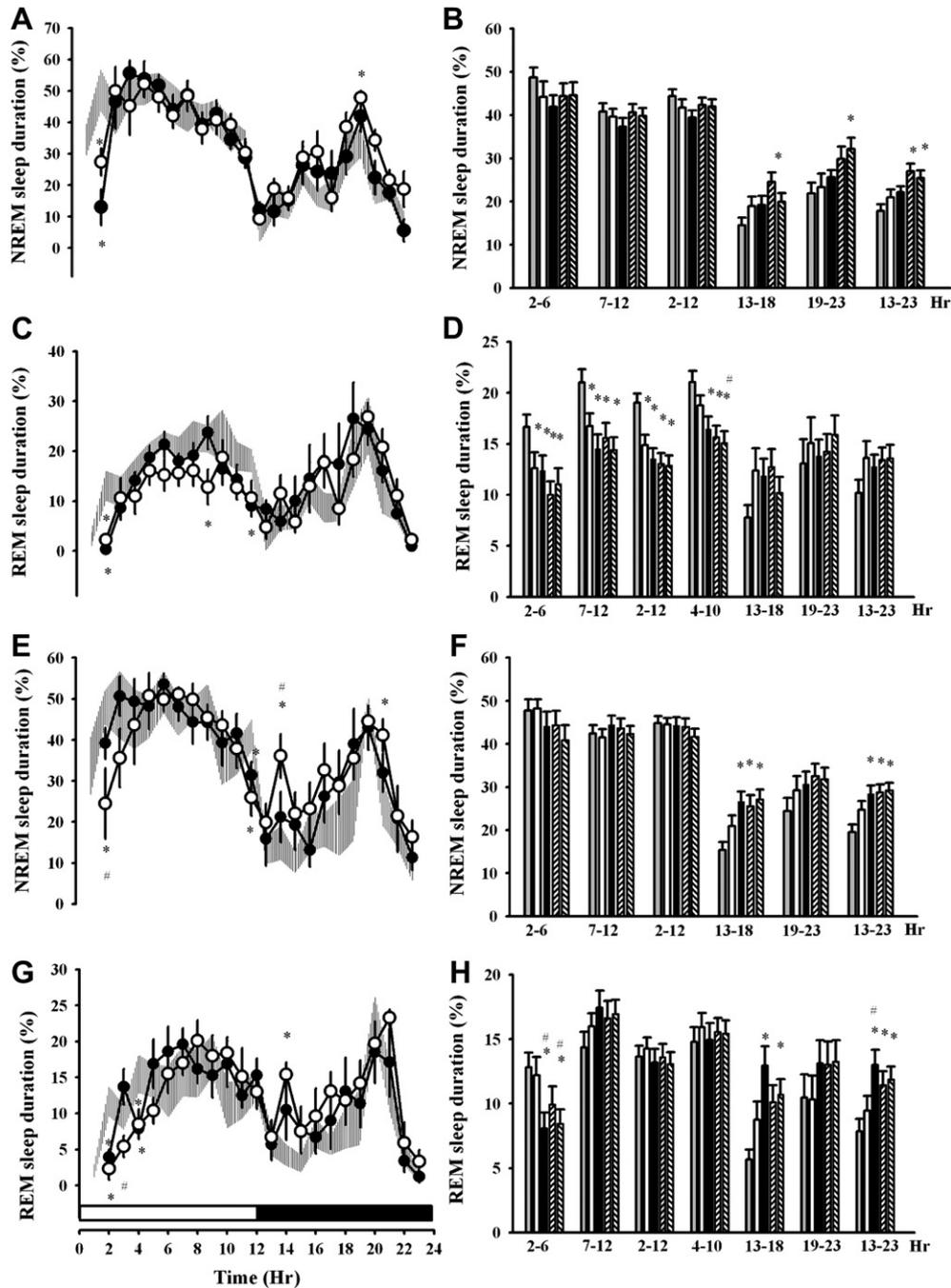


Fig. 5. The alterations of NREM sleep and REM sleep after the RCT (A–D) and sleep deprivation (E–H). Shaded areas represent the values obtained without RCT, closed circles depict the values acquired after the first-day RCT, and open circles demonstrate those gained after the fourth-day RCT in panels A and C. Whereas the shaded areas represent the values obtained without SD, closed circles depict the values acquired after the first-day SD, and open circles demonstrate those gained after the fourth-day SD in panels E and G. The bars on the histograms from left to right demonstrate the DMSO control, DMSO + day-1 RCT/or day-1 SD, DMSO + day-2 RCT/or day-2 SD, DMSO + day-3 RCT/or day-3 SD, and DMSO + day-4 RCT/or day-4 SD, respectively. *represents the statistically significant difference when compared to the values obtained after DMSO control, and # depicts the statistically significant difference when compared to the values obtained after day-1 RCT/or day-1 SD. The dark and open portions of the horizontal bars represent the dark and light periods of the 12:12 h light:dark cycle.

anxiety and anxiety-induced sleep disturbances. Our results indicate that the time spent in the centre arena of the OF decreased with the numbers of RCT exposure, immobilization time was increased, and the total distance of movement and movement distance in the centre arena were consistently decreased following the repeated OF exposure, suggesting that the habituation does not exist when performing the OF in these combination tests. Further analysis revealed that the anxiety level, indicated as the decrease of

time in the centre arena of the OF, was higher during the first 25-min OF exposure in day-2 and day-3, and increased during the second 25-min in the latter days (day-3 and day-4). The EPM also exhibited sustained anxiousness by decreasing time spent in open arms and reducing frequency of entry to the open arms after repetitive trials. In addition, consistent increases of the urination and defecation were observed after exposing to RCT. These observations suggest that the RCT did not cause rats to habituate

Table 2

Effects of RCT, CBD and sleep deprivation on the sleep–wake architecture parameters of rats.

Manipulation ^d	Hour	L:D cycle ^e	Number of bouts ^a			Bout duration ^b			Transitions ^c
			WAKE ^f	NREMS ^f	REMS ^f	WAKE	NREMS	REMS	
Vehicle control (DMSO)	2–12	L	6.7 ± 0.4	11.0 ± 0.2	5.4 ± 0.4	3.0 ± 0.2	2.5 ± 0.2	2.1 ± 0.1	42.9 ± 1.9
DMSO + RCT day1	2–12	L	6.5 ± 0.2	10.3 ± 0.3	4.7 ± 0.3	5.1 ± 0.8*	2.4 ± 0.2	1.8 ± 0.1	41.0 ± 2.7
DMSO + RCT day3	2–12	L	7.4 ± 0.4	11.5 ± 0.9	4.2 ± 0.5	4.0 ± 0.6	2.3 ± 0.2	1.6 ± 0.2*	41.9 ± 3.9
DMSO + RCT day4	2–12	L	7.3 ± 0.5	11.2 ± 0.6	4.5 ± 0.5	3.9 ± 0.5	2.3 ± 0.2	1.5 ± 0.2*	43.0 ± 3.1
Vehicle control (DMSO)	2–12	L	7.5 ± 0.5	11.5 ± 0.8	4.3 ± 0.3	4.6 ± 1.0	2.2 ± 0.1	1.7 ± 0.2	46.2 ± 3.8
DMSO + RCT day1	2–12	L	7.2 ± 0.6	10.5 ± 0.9	3.9 ± 0.3	6.6 ± 1.0	2.5 ± 0.2	1.7 ± 0.2	40.6 ± 1.5
0.5 µg CBD + RCT day3	2–12	L	7.2 ± 0.4	10.0 ± 0.4	3.6 ± 0.3	5.7 ± 0.9	2.4 ± 0.1	1.7 ± 0.1	42.8 ± 2.0
DMSO + RCT day4	2–12	L	6.9 ± 0.3	10.1 ± 0.5	3.7 ± 0.3	6.7 ± 1.3	2.5 ± 0.2	1.7 ± 0.2	41.2 ± 2.1
Vehicle control (DMSO)	2–12	L	7.8 ± 0.4	11.3 ± 0.2	4.3 ± 0.3	3.5 ± 0.1	2.2 ± 0.1	2.1 ± 0.1	41.4 ± 0.7
DMSO + RCT day1	2–12	L	6.7 ± 0.4	9.8 ± 0.5*	3.5 ± 0.4	7.6 ± 0.8*	2.3 ± 0.1	2.1 ± 0.1	32.8 ± 2.0*
1.0 µg CBD + RCT day3	2–12	L	7.0 ± 0.4	10.2 ± 0.3	4.1 ± 0.2	7.6 ± 0.8*	2.3 ± 0.2	2.2 ± 0.1	36.8 ± 1.7
DMSO + RCT day4	2–12	L	6.4 ± 0.4*	10.0 ± 0.4*	4.0 ± 0.2	6.7 ± 1.0*	2.4 ± 0.2	2.3 ± 0.2	36.2 ± 2.5
Vehicle control (DMSO)	2–12	L	8.0 ± 0.2	12.1 ± 0.4	4.1 ± 0.5	3.1 ± 0.2	2.3 ± 0.2	2.1 ± 0.1	45.0 ± 1.3
SD day1	2–12	L	7.1 ± 0.3	11.0 ± 0.6	4.0 ± 0.4	3.9 ± 0.4	2.5 ± 0.1	2.2 ± 0.2	39.0 ± 1.7*
SD day3	2–12	L	6.9 ± 0.5	10.8 ± 0.6	3.6 ± 0.2	5.5 ± 1.4	2.5 ± 0.1	2.1 ± 0.2	39.0 ± 2.7*
SD day4	2–12	L	7.1 ± 0.5	10.4 ± 0.7	3.5 ± 0.1	4.0 ± 0.8	2.2 ± 0.1	1.9 ± 0.1	37.5 ± 2.3*

Values are Means ± S.E.M. *denotes a statistically significant difference ($p < 0.05$) between values obtained after administration of vehicle (DMSO) and those obtained after manipulations.

^a Number of bouts per hour (mean ± SEM) for each vigilance state.

^b Mean (±SEM) bout duration (min) for each vigilance state.

^c Number of transitions from one behavioural state to another (mean ± SEM) per hour.

^d Experimental manipulation.

^e Period of the light:dark cycle immediately prior to which injections were given: L = light period.

^f Vigilance states: WAKE, wakefulness; NREMS, non-rapid eye movement sleep; REMS, rapid eye movement sleep.

anxiety/stress and can act as a suitable model to induce persistent anxiety in rats.

Our results demonstrated that 1-h of RCT decreased NREM sleep during the first hour after each time of exposure, and the decrease of NREM sleep gradually declined when the times of exposure increased. REM sleep was decreased during the first hour after RCT, and the decrease of REM sleep during the time block of hours 4–10 was predominantly enhanced in accordance with the increased exposure numbers. There was no rebound of NREM or REM sleep obtained after the manipulation of RCT. These sleep alterations might resemble the features of decreased total sleep time and shorter REM sleep time observed in PTSD patients. The reduction of NREM sleep during the first hour after 1-h sleep deprivation only reached statistical significance after deprivation in day-4 and a rebound in NREM sleep was observed during the subsequent dark period. One-hour sleep deprivation also decreased REM sleep during the immediate 3 h after deprivation and a REM sleep rebound was also found in the dark period. Our previous results demonstrate that 1-h acute stressor, the physical restraint, applied at the beginning of the light period (but not the dark period) increases waking and decreases REM sleep immediately after the restraint, and does not dramatically alter NREM sleep (Chang and Opp, 2002). The initial decrease of REM sleep during the initial 3 h after 1-h sleep deprivation, considered as a mild stressor, observed in the current study is consistent with our previous findings (Chang and Opp, 2002). Others have reported that physical restraint primarily induces a REM sleep rebound; Rampin et al. reported that a 2-h period of physical restraint applied to rats at the beginning of the dark period induces a significant increase in REM sleep during the remaining 10 h of the dark period (Rampin et al., 1991). The REM sleep rebound after sleep deprivation might be due to the effect of acute stress, which was not observed after RCT manipulation. These SD-induced alterations in NREM and REM sleep differ from those acquired after RCT, suggesting the effect of RCT on the sleep alterations was not primarily due to the effects of

sleep deprivation. Decrement in REM sleep is thought to be an indicator of the anxiety level. Tang et al. (2004) have demonstrated that the anxiousness induced by OF decreases REM sleep which is greater in more anxious mice, such as BALB/cj mice; whereas the exploration activity in OF, associated with the delayed REM increase, increases greater in less anxious mice (e.g. C57BL/6J and CB6F1/J mice) (Tang et al., 2004). The gradual and continued decrease of REM sleep during hours 4–10, when rats were exposed to the 1-h RCT for four consecutive days, was consistent with the increased anxiety-like behaviours observed from the OF and EPM, further indicating the model of RCT resembles the features of REM disruption in PTSD patients.

The amygdala appears to be a critical brain structure which involves in emotional, behavioural, and physiological responses associated with fear and anxiety (Davis, 1992; Kim and Jung, 2006). During acquisition of fear conditioning, sensory information is transmitted from thalamus and sensory cortices to the lateral amygdala, and then is projected to the CeA, which is further transmitted to the hypothalamus and brainstem structures where there is response to autonomic and visceral fear [review (Germain et al., 2008)]. Growing evidence also indicates that the amygdala is an important modulator in both NREM and REM sleep, although it is not the primary brain region involved in sleep–wake regulation. Electrical stimulation of CeA suppresses delta wave activity in the frontal cortex and increases arousal (Kapp et al., 1994), and inactivation of CeA with tetrodotoxin decreases REM sleep and increases slow wave sleep (Tang et al., 2005). CBD is the first compound isolated from the cannabis plant and exhibits a broad pharmacological profile, including anti-convulsion, sedation, anti-anxiety, hypnotic effect, anti-psychosis and anti-inflammation (Mechoulam et al., 2002). Those pharmacological properties are more predominant for therapeutic purposes than other active compounds extracted from *C. sativa*, such as THC, because of its non-psychoactive effect (Grotenhermen, 2006). Systemic administration of CBD (2.5–10 mg/kg) exhibits an anxiolytic-like effect

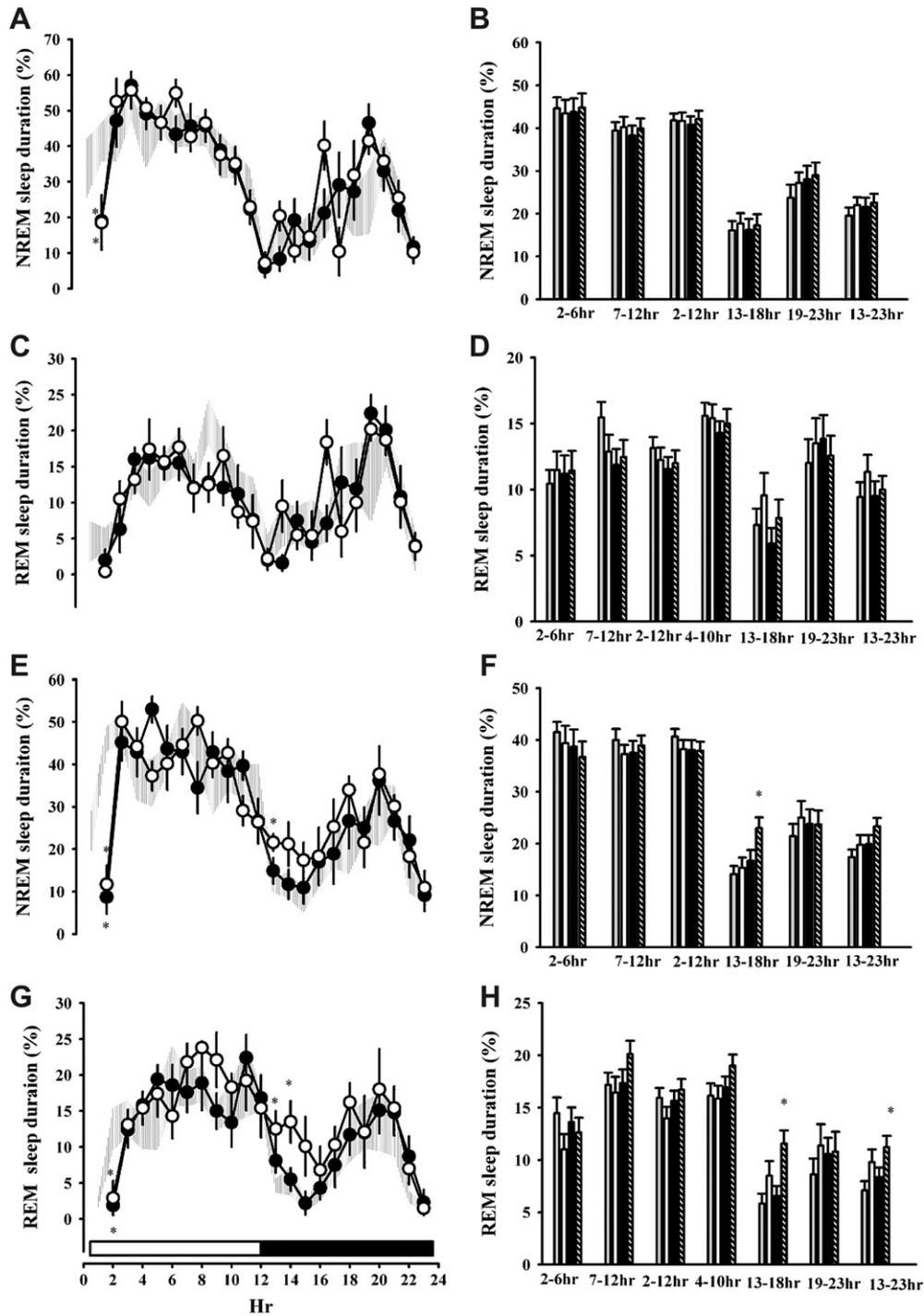


Fig. 6. The effects of CBD on RCT-induced sleep alterations. Panels A–D represent the data obtained from the low-dose (0.5 µg) CBD group and Panels E–H demonstrate the values acquired from the high-dose (1.0 µg) CBD group. Shaded areas represent the values obtained after DMSO administration but without RCT, closed circles depict the values acquired after the CBD + day-3 RCT, and open circles demonstrate those gained after DMSO + day-4 RCT in panels A, C, E and G. The bars of the histograms from left to right demonstrate the DMSO control, DMSO + day-1 RCT, CBD + day-3 RCT, and DMSO + day-4 RCT, respectively. *represents the statistically significant difference when compared to the values obtained after the DMSO control.

evaluated by the EPM assay (Guimaraes et al., 1990). CBD improves stress-induced avoidance learning and decreases response suppression in a punished response task (Musty, 1984). Comparing the anxiolytic effect of CBD with ipsapirone (a 5-HT_{1A} partial agonist) and diazepam reveals that three compounds are active with similar efficacies, although the dose of CBD needed is considerably higher than two other drugs (Zuardi et al., 1993). The

effects of CBD on sleep–wake regulation *per se* have been reported. Systemic administration of CBD reduces sleep (Monti, 1977), and intraventricular administration of CBD at the beginning of the light period increases wakefulness and decreases REM sleep (Murillo-Rodríguez et al., 2006). Furthermore, our previous results demonstrated that microinjection of CBD directly into the CeA prior to the beginning of the light period dose-dependently decreases NREM

sleep with limited effect on REM sleep suppression (Yi et al., 2008). However, the effect of CBD on anxiety-induced sleep–wake alteration hasn't been determined. Our current results indicate that the anxiety behaviours, including the decrease of time spent during the centre arena of OF and decrease of time exploring in the open arms of EPM, were suppressed after administration of CBD into the CeA. The frequency of entering the enclosed arms of EPM was also decreased by CBD. These observations further confirmed the anxiolytic effect of CBD. Our results also demonstrated that the RCT-induced REM suppression during hours 4–10 of the light period was blocked by microinjection of CBD directly into the CeA. Comparing the effects of CBD administered into the CeA on spontaneous sleep regulation (decrease of NREM sleep with limited suppression in REM sleep), present results suggest CBD blocks anxiety-induced REM sleep alteration via its anxiolytic effect, rather than via sleep regulation *per se*. The effect of CBD in anxiolytic might be due to the inhibition of endogenous endocannabinoid (anandamide) uptake and hydrolysis or the anti-oxidative effect (Mechoulam et al., 2002). Nevertheless, the underlying mechanism is worthy for further investigation. Furthermore, the decreases of NREM sleep and REM sleep during the first hour after RCT were not altered by CBD and a rebound of REM sleep appeared after CBD administration, suggesting the initial suppressions of NREM and REM sleep were caused by the sleep deprivation, since these features were similar to those of sleep deprivation.

In summary, our current results suggest that RCT may become a suitable rodent model to simulate the REM alteration after the PTSD. CBD may block anxiety-induced REM sleep alteration via its anxiolytic effect, rather than via sleep regulation *per se*.

Statement of interest

None. Authors have indicated no financial conflicts of interest.

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References

- American Psychiatry Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, fourth ed. American Psychiatry Association, Washington DC.
- Anderson, D.J., Noyes, R., Crowe, R.R., 1984. A comparison of panic disorder and generalized anxiety disorder. *Am. J. Psychiatry* 141, 572–575.
- Brady, K.T., Sinha, R., 2005. Co-occurring mental and substance use disorders: the neurobiological effects of chronic stress. *Am. J. Psychiatry* 162, 1483–1493.
- Breslau, N., Roth, T., Burduvali, E., Kapke, A., Schultz, L., Roehrs, T., 2004. Sleep in lifetime posttraumatic stress disorder: a community-based polysomnographic study. *Arch. Gen. Psychiatry* 61, 508–516.
- Chang, F.C., Opp, M.R., 1998. Blockade of corticotropin-releasing hormone (CRH) receptors reduces spontaneous waking in the rat. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 275, R793–R802.
- Chang, F.C., Opp, M.R., 2002. Role of corticotrophin-releasing hormone in stressor-induced alterations of sleep in rat. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 283, R400–R407.
- Chevalayre, V., Takahashi, K.A., Castillo, P.E., 2006. Endocannabinoid-mediated synaptic plasticity in the CNS. *Annu. Rev. Neurosci.* 29, 37–76.
- Cholieris, E., Thomas, A.W., Kavaliers, M., Prato, F.S., 2001. A detailed ethological analysis of the mouse open field test: effects of diazepam, chlordiazepoxide and an extremely low frequency pulsed magnetic field. *Neurosci. Biobehav. Rev.* 25, 235–260.
- Crippa, J.A., Zuardi, A.W., Garrido, G.E., Wichert-Ana, L., Guarnieri, R., Ferrari, L., Azevedo-Marques, P.M., Hallak, J.E., McGuire, P.K., Filho Busatto, G., 2004. Effects of cannabidiol (CBD) on regional cerebral blood flow. *Neuropharmacology* 29, 417–426.
- Davis, M., 1992. The role of the amygdala in fear and anxiety. *Annu. Rev. Neurosci.* 15, 353–375.
- ElSohly, M.A., 2002. Chemical constituents of cannabis. In: Grotenhermen, F., Russo, E. (Eds.), *Cannabis and Cannabinoids. Pharmacology, Toxicology, and Therapeutic Potential*. Haworth Press, Binghamton/New York, pp. 27–36.
- Fuller, K.H., Waters, W.F., Scott, O., 1994. An investigation of slow-wave sleep processes in chronic PTSD patients. *J. Anxiety Disord.* 8, 227–236.
- Fusar-Poli, P., Allen, P., Bhattacharyya, S., Crippa, J.A., Mechelli, A., Borgwardt, S., Martin-Santos, R., Seal, M.L., O'Carroll, C., Atakan, Z., Zuardi, A.W., Philip McGuire, P., 2010. Modulation of effective connectivity during emotional processing by Delta 9-tetrahydrocannabinol and cannabidiol. *Int. J. Neuropsychopharmacol.* 13, 421–432.
- Germain, A., Buysse, D.J., Nofzinger, E., 2008. Sleep-specific mechanisms underlying posttraumatic stress disorder: integrative review and neurobiological hypotheses. *Sleep Med. Rev.* 12, 185–195.
- Graeff, F.G., Netto, C.F., Zangrossi Jr., H., 1998. The elevated T-maze as an experimental model of anxiety. *Neurosci. Biobehav. Rev.* 23, 237–246.
- Grotenhermen, F., 2006. Cannabinoids and the endocannabinoid system. *Cannabinoids* 1, 10–14.
- Guimaraes, F.S., Chiaretti, T.M., Graeff, F.G., Zuardi, A.W., 1990. Antianxiety effect of cannabidiol in the elevated plus-maze. *Psychopharmacology* 100, 558–589.
- Hall, C.S., 1936. Emotional behavior in the rat. III. The relationship between emotionality and ambulatory activity. *J. Comp. Psychol.* 22, 345–352.
- Harvey, A.G., Bryant, R.A., 1998. The relationship between acute stress disorder and posttraumatic stress disorder: a prospective evaluation of motor vehicle accident survivors. *J. Consult. Clin. Psychol.* 66, 507–512.
- Hefez, A., Metz, L., Lavie, P., 1987. Long-term effects of extreme situational stress on sleep and dreaming. *Am. J. Psychiatry* 144, 344–347.
- Horowitz, M.J., Wilner, N., Kaltreider, N., Alvarez, W., 1980. Signs and symptoms of posttraumatic stress disorder. *Arch. Gen. Psychiatry* 37, 85–92.
- Ivinskis, A., 1970. A study of validity of open-field measures. *Aust. J. Psychol.* 22, 175–183.
- Kapp, B.S., Supple Jr., W.F., Whalen, P.J., 1994. Effects of electrical stimulation of the amygdaloid central nucleus on neocortical arousal in the rabbit. *Behav. Neurosci.* 108, 81–93.
- Kim, J.J., Jung, M.W., 2006. Neural circuits and mechanisms involved in Pavlovian fear conditioning: a critical review. *Neurosci. Biobehav. Rev.* 30, 188–202.
- Koren, D., Amon, I., Lavie, P., Klein, E., 2002. Sleep complaints as early predictors of posttraumatic stress disorder: a 1-year prospective study of injured survivors of motor vehicle accidents. *Am. J. Psychiatry* 159, 855–857.
- Lavie, P., Hefez, A., Halperin, G., Enoch, D., 1979. Long-term effects of traumatic war-related events on sleep. *Am. J. Psychiatry* 136, 175–178.
- Makino, J., Kato, K., Maes, F.W., 1991. Temporal structure of open field behavior in inbred strains of mice. *Jpn. Psychol. Res.* 33, 145–152.
- Mechoulam, R., 1970. Marijuana chemistry. *Science* 168, 1159–1166.
- Mechoulam, R., Parker, L.A., Ruth, G., 2002. Cannabidiol: an overview of some pharmacological aspects. *J. Clin. Pharmacol.* 42, 115–195.
- Mellman, T.A., Bustamante, V., Fins, A., Pigeon, W.R., Nolan, B., 2002. REM sleep and early development of posttraumatic stress disorder. *Am. J. Psychiatry* 159, 1696–1701.
- Mellman, T.A., David, D., Bustamante, V., Torres, J., Fins, A., 2001. Dreams in the acute aftermath of trauma and their relationship to PTSD. *J. Trauma. Stress* 14, 241–247.
- Mellman, T.A., Davis, G.C., 1985. Combat-related flashbacks in posttraumatic stress disorder: phenomenology and similarity to panic attacks. *J. Clin. Psychiatry* 46, 379–382.
- Mikulincer, M., Glaubman, H., Wasserman, O., Porat, A., 1989. Control-related beliefs and sleep characteristics of posttraumatic stress disorder patients. *Psychol. Rep.* 65, 567–576.
- Monti, J.M., 1977. Hypnotic-like effects of cannabidiol in the rat. *Psychopharmacology* 55, 263–265.
- Murillo-Rodríguez, E., Millán-Aldaco, D., Palomero-Rivero, M., Mechoulam, R., Drucker-Colín, R., 2006. Cannabidiol, a constituent of *Cannabis sativa*, modulates sleep in rats. *FEBS Lett.* 580, 4337–4345.
- Musty, R., 1984. Possible anxiolytic effects of cannabidiol. In: Agurell, S., Dewey, W.L., Willette, R.E. (Eds.), *The Cannabinoids: Chemical, Pharmacological and Therapeutic Aspects*. Academic Press, New York, pp. 795–813.
- Neylan, T.C., Marmar, C.R., Matzler, T.J., Weiss, D.S., Zatzick, D.F., Delucchi, K.L., Wu, R.M., Schoenfeld, F.B., 1998. Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. *Am. J. Psychiatry* 155, 929–933.
- Pawlyk, A.C., Morrison, A.R., Ross, R.J., Brennan, F.X., 2008. Stress-induced changes in sleep in rodents: models and mechanisms. *Neurosci. Biobehav. Rev.* 32, 99–117.
- Paxinos, G., Watson, C., 1998. *The Rat Brain in Stereotaxic Coordinates*, fourth ed. Academic Press, San Diego.
- Pellow, S., Chopin, P., File, S.E., Briley, M., 1985. Validation of open:closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. *J. Neurosci. Methods* 14, 149–167.
- Pickens, J.T., 1981. Sedative activity of cannabis in relation to its Delta-1-trans-tetrahydrocannabinol and cannabidiol content. *Br. J. Pharmacol.* 72, 649–656.
- Prut, L., Belzung, C., 2003. The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: a review. *Eur. J. Pharmacol.* 463, 3–33.
- Rampin, C., Cesuglio, R., Chastrette, N., Jouvet, M., 1991. Immobilisation stress induces a paradoxical sleep rebound in rat. *Neurosci. Lett.* 126, 113–118.

- Ross, R.J., Ball, W.A., Dinges, D.F., Kribbs, N.B., Morrison, A.R., Silver, S.M., Mulvaney, F.D., 1994. Rapid eye movement sleep disturbance in posttraumatic stress disorder. *Biol. Psychiatry* 35, 195–202.
- Sanford, L.D., Tejani-Butt, S.M., Ross, R.J., Morrison, A.R., 1995. Amygdaloid control of alerting and behavioral arousal in rats: involvement of serotonergic mechanisms. *Arch. Ital. Biol.* 134, 81–99.
- Tang, X., Yang, L., Liu, X., Sanford, L.D., 2005. Influence of tetrodotoxin inactivation of the central nucleus of the amygdala on sleep and arousal. *Sleep* 28, 923–930.
- Tang, X., Xiao, J., Liu, X., Sanford, L.D., 2004. Strain differences in the influence of open field exposure on sleep in mice. *Behav. Brain Res.* 154, 137–147.
- Treit, D., Menard, J., Royan, C., 1993. Anxiogenic stimuli in the elevated plus-maze. *Pharmacol. Biochem. Behav.* 44, 463–469.
- Welker, W.I., 1957. "Free" versus "forced" exploration of a novel situation by rats. *Psychol. Rep.* 3, 95–108.
- Yi, P.L., Hsiao, Y.T., Tsai, C.H., Jan, T.R., Lu, C.Y., Chang, F.C., 2008. Serotonergic system in the central nucleus of amygdala mediates cannabidiol-induced sleep alteration. *Open Sleep J.* 1, 58–68.
- Zuardi, A.W., Cosme, R.A., Graeff, F.G., Guimaraes, F.S., 1993. Effects of ipsapirone and cannabidiol on human experimental anxiety. *J. Psychopharmacol.* 7, 82–88.

Effectiveness of Cannabidiol Oil for Pediatric Anxiety and Insomnia as Part of Posttraumatic Stress Disorder: A Case Report

Scott Shannon, MD, ABIHM; Janet Opila-Lehman, ND

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ABSTRACT

Introduction: Anxiety and sleep disorders are often the result of posttraumatic stress disorder and can contribute to an impaired ability to focus and to demonstration of oppositional behaviors.

Case Presentation: These symptoms were present in our patient, a ten-year-old girl who was sexually abused and had minimal parental supervision as a young child under the age of five. Pharmaceutical medications provided partial relief, but results were not long-lasting, and there were major side effects. A trial of cannabidiol oil resulted in a maintained decrease in anxiety and a steady improvement in the quality and quantity of the patient's sleep.

Discussion: Cannabidiol oil, an increasingly popular treatment of anxiety and sleep issues, has been documented as being an effective alternative to pharmaceutical medications. This case study provides clinical data that support the use of cannabidiol oil as a safe treatment for reducing anxiety and improving sleep in a young girl with posttraumatic stress disorder.

INTRODUCTION

Cannabidiol (CBD) oil is a naturally occurring constituent of industrial hemp and marijuana, which are collectively called cannabis. CBD oil is 1 of at least 85 cannabinoid compounds found in cannabis and is popular for its medicinal benefits. After tetrahydrocannabinol (THC), CBD oil is the second-most-abundant component of cannabis. Other names for CBD oil include CBD-rich hemp oil, hemp-derived CBD oil, or CBD-rich cannabis oil. Considered to be generally safe, CBD has been used medicinally for decades. However, CBD is not medical marijuana and should be distinguished from high-CBD strains

of medical marijuana, which do contain THC, such as “Charlotte’s Web.”

The most abundant compound in cannabis, THC is also a cannabinoid. The THC component induces the psychoactive effect, “high.” A cannabis plant has different amounts of CBD and THC depending on the strain and thus provides different recreational or medicinal effects. The cannabinoid profile of industrial hemp or medical marijuana is ideal for people looking for the medical benefits of CBD without the “high” of the THC.

The mechanism of action of CBD is multifold.¹⁻³ Two cannabinoid receptors are known to exist in the human body: CB1 and CB2 receptors. The CB1 receptors are located mainly in the brain and modulate neurotransmitter release in a manner that prevents excessive neuronal activity (thus calming and decreasing anxiety), as well as reduces pain, reduces inflammation, regulates movement and posture control, and regulates sensory perception, memory, and cognitive function.^{4,2} An endogenous ligand, anandamide, which occurs naturally in our bodies, binds to the CB1 receptors through the G-protein coupling system. CBD has an indirect effect on the CB1 receptors by stopping the enzymatic breakdown of anandamide, allowing it to stay in the system longer and provide medical benefits.⁴ CBD has a mild effect on the CB2 receptors, which are located in the periphery in lymphoid tissue. CBD helps to mediate the release of cytokines from the immune cells in a manner that helps to reduce inflammation and pain.²

Other mechanisms of action of CBD include stimulation of vanilloid pain receptors (TRPV-1 receptor), which are known to mediate pain perception, inflammation, and body temperature.⁵ In addition, CBD may exert its anti-anxiety effect by

activating adenosine receptors which play a significant role in cardiovascular function and cause a broad anti-inflammatory effect throughout the body.⁵ At high concentrations, CBD directly activates the 5-HT1A serotonin receptor, thereby conferring an antidepressant effect.⁶ Cannabidiol has been found to be an antagonist at the potentially new third cannabinoid receptor, GPR55, in the caudate nucleus and putamen, which if stimulated may contribute to osteoporosis.⁷

Since the 1940s, a considerable number of published articles have dealt with the chemistry, biochemistry, pharmacology, and clinical effects of CBD.⁸ The last decade has shown a notable increase in the scientific literature on CBD, owing to its identification for reducing nausea and vomiting, combating psychotic disorders, reducing inflammation, decreasing anxiety and depression, improving sleep, and increasing a sense of well-being.⁹⁻¹² Findings presented at the 2015 International Cannabinoid Research Society at its 25th Annual Symposium reported the use of CBD as beneficial for kidney fibrosis and inflammation, metabolic syndrome, overweight and obesity, anorexia-cachexia syndrome, and modification of osteoarthritic and other musculoskeletal conditions.¹³⁻¹⁶

Although studies have demonstrated the calming, anti-inflammatory, and relaxing effects of CBD, clinical data from actual cases is minimal. This case study offers evidence that CBD is effective as a safe alternative treatment to traditional psychiatric medications for reducing anxiety and insomnia.¹⁷

CASE PRESENTATION

A ten-year-old girl presented in January 2015 for a reevaluation of behaviors related to her diagnosis of posttraumatic stress disorder (PTSD) secondary to sexual

Scott Shannon, MD, ABIHM, is an Assistant Clinical Professor of Psychiatry at the University of Colorado School of Medicine in Fort Collins. E-mail: scottshannon@cowisp.net. Janet Opila-Lehman, ND, is a Naturopathic Physician at the Wholeness Center in Fort Collins, CO. E-mail: j.opila.lehman@gmail.com.

abuse. Her chief issues included anxiety, insomnia, outbursts at school, suicidal ideation, and self-destructive behaviors. Her grandmother, who has permanent custody of the patient and her younger brother, accompanied her.

Our patient had been seen for an initial evaluation in January 2012 and received a diagnosis of PTSD secondary to sexual abuse on the basis of her history, clinical observations, and behaviors (Table 1).

Her father had died 6 months earlier in a motor vehicle accident, and our patient's maternal grandparents became her permanent guardians. Before her father's death, our patient had no supervision from her father and very little supervision from her mother. An 11-year-old boy had molested her when she was 3 years old. Her medical history included her mother having methadone addiction, alcoholism, bipolar disorder, and depression. Her mother used

marijuana her entire pregnancy with the girl. The patient presented in January 2012 as displaying aggressive, disobedient, impulsive, and sexually inappropriate behaviors. She also demonstrated low self-esteem and anxiety and had poor sleep (restless, interrupted, and unable to sleep alone).

Workup during 2012 included laboratory studies, which ruled out a thyroid dysfunction and an iron or vitamin D deficiency. The patient was started on a

Table 1. Timeline

Date	Presentation	Medications	Supplements	Other
January 31, 2012	New evaluation: 7.5-year-old girl. History of sexual abuse and neglect. Issues: Insomnia, sexual behaviors. Diagnosis: PTSD secondary to sexual abuse.	None	Melatonin, 1 mg/night	February 14, 2012, laboratory values: TSH, 2.46 mIU/L (reference range, 0.47-4.68 mIU/L); ferritin: 21 ng/mL (reference range, 10-150 ng/mL). February 16, 2012, laboratory values: Vitamin D ₃ : 39 ng/mL (reference range, 20-50 ng/mL)
February 20, 2012	Sleeping 2-3 hours/night. Started counseling; Cooperative and good behavior at counseling session. Anxious, traumatized.	Clonidine, 0.05 mg (half tablet) at bedtime	Inositol, 3 g 3 times/d; EPA fish oil, 500 mg/d	Eye movement desensitization and reprocessing therapy recommended
February 22, 2012	Did not do well with clonidine because of hallucinations, so she discontinued that treatment. Behavior still very rough; sleep poor.	Started imipramine therapy, 25 mg at bedtime		March 7, 2012: ECG was normal
August 8, 2012 ^a	Good summer. In play therapy. Overall better sleep and energy with imipramine therapy. Patient's 6-year-old brother also now in therapy.	Imipramine, 25 mg at bedtime		
January 21, 2015	Returned for evaluation and treatment after 3 years. Suicidal ideation; cut self on leg; defiant and stubborn. Had psychotherapy 3 years straight twice a month. Sleeps with brother; can't sleep alone.	Off all medications for past 18 months	Melatonin, 5 mg; St John's wort, 450 mg twice/d; magnesium, 300 mg/d; diphenhydramine, 25 mg/night	
February 16, 2015	Hard to manage. Has outbursts at school.		Magnesium and St John's wort: stopped treatment; EPA fish oil, 750 mg/d; diphenhydramine, 25 mg/night	February 11, 2015: Normal cortisol and DHEA levels
March 16, 2015	Better overall. Started animal-assisted therapy.		EPA fish oil, 750 mg/d; diphenhydramine, 25 mg/night	Started a regimen of CBD oil, 25 mg (1 capsule)/d at 6 pm
April 14, 2015	Sleeping better with CBD treatment. Getting biofeedback. Has stomachaches. Mood is more at ease.		EPA fish oil, 750 mg/d; diphenhydramine, 25 mg/night	CBD oil, 25 mg (1 capsule)/d at 6 pm
May 26, 2015	"Ghosts" waking patient up at night.		EPA fish oil, 750 mg/d	CBD oil, 25 mg (1 capsule)/d at 6 pm
July 22, 2015	Sleeping better; able to sleep in own room 3-4 nights/wk.		EPA fish oil, 750 mg/d	CBD liquid, 12 mg (in 4 sublingual sprays)/night; 12 mg more (in 4 sublingual sprays) during the day as needed for anxiety, typically 3 or 4 times/wk
August 24, 2015	Sleeping well. Handling school well.		EPA fish oil, 750 mg/d	CBD oil, 25 mg (1 capsule)/night; CBD liquid, 6-12 mg (in 2-4 sublingual sprays) as needed for anxiety, typically 2 or 3 times/wk

^a There were additional visits in 2012 with no substantial changes.

CBD = cannabidiol; DHEA = dehydroepiandrosterone; ECG = electrocardiogram; EPA = eicosapentaenoic acid; PTSD = posttraumatic stress disorder; TSH = thyroid stimulating hormone.

regimen of 1 mg/night of melatonin, which helped her sleep duration. Three grams of inositol 3 times a day and 500 mg/d of eicosapentaenoic fish oil were also helpful in reducing her anxiety. A trial of clonidine was implemented, which resulted in hallucinations and thus was discontinued. The patient was switched to a regimen of 25 mg of imipramine at bedtime to decrease her anxiety, which appeared to be helpful. Counseling sessions were started. The patient continued psychotherapy for 3 years, but she was not seen again in our clinic until the return visit in January 2015, when she was not receiving any of her medications and supplements.

CBD oil can be an effective compound to reduce anxiety and insomnia secondary to PTSD.

At the patient's return in January 2015, she demonstrated the same prominent symptoms as at her initial presentation. At that time, the initial treatment included the following supplements and medications to assist with her sleep and anxiety: melatonin, 5 mg/night; magnesium, 300 mg/d; and diphenhydramine (Benadryl), 25 mg/night. Our patient demonstrated slight gains but was still having outbursts at school and was reportedly difficult to manage at home. In addition, her underlying anxiety continued.

Cannabidiol oil was explored as a potential additional treatment to help her insomnia and anxiety, but we deferred for two months while we waited for a response from other interventions. The grandmother preferred reducing the pharmacologic load given her granddaughter's failure to respond long term to psychiatric medications.

In March 2015, CBD oil was recommended as a potential additional treatment to help her insomnia and anxiety, and her grandmother provided full informed consent. Our patient was administered the Sleep Disturbance Scale for Children¹⁸ and the Screen for Anxiety Related Disorders (SCARED)¹⁹ before taking the CBD oil and each month afterward for the next 5 months. Test scores on the Sleep Disturbance Scale for Children and Screen for

Anxiety Related Disorders demonstrated an improvement (Table 2).

A trial of CBD supplements (25 mg) was then initiated at bedtime, and 6 mg to 12 mg of CBD sublingual spray was administered during the day as needed for anxiety. A gradual increase in sleep quality and quantity and a decrease in her anxiety were noted. After 5 months, the patient was sleeping in her own room most nights and handling the new school year with no difficulties. No side effects were observed from taking the CBD oil.

DISCUSSION

Studies repeatedly recognize the prevalence of an anxiety-provoked sleep disorder after a traumatic experience.²⁰ Our patient was definitely experiencing this phenomenon, which was aggravated by daily stressful activities.

The main finding from this case study is that CBD oil can be an effective compound to reduce anxiety and insomnia secondary to PTSD. A review of the literature suggests some benefits from the use of CBD because of its anxiolytic and sleep-inducing effects.⁹ Animal studies support use of this treatment and report that "CBD may block anxiety-induced [rapid eye movement] sleep alteration via its anxiolytic effect on the brain."²¹

The strength of this particular case is that our patient was receiving no pharmaceutical medications (other than non-prescription diphenhydramine) but only nutritional supplements and the CBD oil to control her symptoms. Her scores on the sleep scale and the anxiety scale consistently and steadily decreased during a period of 5 months (see Table 2). She

was ultimately able to sleep through the night most nights in her own room, was less anxious at school and home, and displayed appropriate behaviors. The patient's grandmother (her caregiver) reported: "My granddaughter's behaviors are definitely better being on the CBD. Her anxiety is not gone, but it is not as intense and she is much easier to be around. She now sleeps in her own room most of the time, which has never happened before."

Further study will need to be conducted to determine the permanency of our patient's positive behaviors and how long she will need to continue taking the CBD oil. We do not have a reasonable foundation to recommend dosing from the scientific literature. However, in our experience, this supplement given 12 mg to 25 mg once daily appears to provide relief of key symptoms with minimal side effects. Our patient did not voice any complaints or discomfort from the use of CBD. We routinely asked about headache, fatigue, and change in appetite or agitation in addition to conducting a routine psychiatric evaluation. Although CBD is considered generally safe,¹⁷ the long-term effects are yet to be studied.

The ultimate goal is to gradually taper her off the use of CBD oil and transition our patient into lifelong coping strategies such as yoga, meditation, and various other therapeutic activities. ❖

^a GW Pharmaceuticals is the founder of the Cannabinoid Research Institute, directed by Philip Robson, MD. Further research articles listed.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Table 2. Patient's clinical progress in sleep and anxiety

Date of visit	Sleep scale score ^a	SCARED score ^b
March 16, 2015	59	34
May 25, 2015	42	24
July 22, 2015	41	19
August 24, 2015	37	16
September 22, 2015	38	18

^a A score of more than 50 is considered indicative of a sleep disorder on the Sleep Disturbance Scale for Children.

^b A SCARED score over 25 indicates a high probability of a childhood anxiety disorder. SCARED = Screen for Anxiety Related Disorders.

References

- Campos AC, Moreira FA, Gomes FV, Del Bel EA, Guimarães FS. Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders. *Philos Trans R Soc Lond B Biol Sci* 2012 Dec 5;367(1607):3364-78. DOI: <http://dx.doi.org/10.1098/rstb.2011.0389>.
- Mechanism of action [Internet]. Cambridge, United Kingdom: GW Pharmaceuticals plc; c2014 [cited 2015 Aug]. Available from: www.gwpharm.com/mechanism-of-action.aspx.
- McPartland JM, Guy G. The evolution of cannabis and coevolution with the cannabinoid receptor—a hypothesis. In: Guy GW, Whittle BA, Robson PJ, editors. *The medicinal uses of cannabis and cannabinoids*. 1st ed. London, United Kingdom: Pharmaceutical Press; 2004. p 71-102.
- Leweke FM, Piomelli D, Pahlisch F, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry* 2012 Mar 20;2:e94. DOI: <http://dx.doi.org/10.1038/tp.2012.15>.
- Lee MA. CBD: how it works. O'Shaughnessy's [Internet] 2011 Autumn [cited 2016 Apr 26]:14. Available from: www.os-extra.cannabisclinicians.org/wp-content/uploads/2012/07/CBDiary21.pdf.
- Crippa JA, Derenusson GN, Ferrari TB, et al. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. *J Psychopharmacol* 2011 Jan;25(1):121-30. DOI: <http://dx.doi.org/10.1177/0269881110379283>.
- McHugh D, Tanner C, Mechoulam R, Pertwee RG, Ross RA. Inhibition of human neutrophil chemotaxis by endogenous cannabinoids and phytocannabinoids: evidence for a site distinct from CB1 and CB2. *Mol Pharmacol* 2008 Feb;73(2):441-50. DOI: <http://dx.doi.org/10.1124/mol.107.041863>.
- Zhornitsky S, Potvin S. Cannabidiol in humans—the quest for therapeutic targets. *Pharmaceuticals (Basel)* 2012 May 21;5(5):529-52. DOI: <http://dx.doi.org/10.3390/ph5050529>.
- Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Rev Bras Psiquiatr* 2008 Sep;30(3):271-80. DOI: <http://dx.doi.org/10.1590/s1516-44462008000300015>.
- Burstein S. Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. *Bioorg Med Chem* 2015 Apr 1;23(7):1377-85. DOI: <http://dx.doi.org/10.1016/j.bmc.2015.01.059>.
- Fernández-Ruiz J, Sagredo O, Pazos MR, et al. Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid? *Br J Clin Pharmacol* 2013 Feb;75(2):323-33. DOI: <http://dx.doi.org/10.1111/j.1365-2125.2012.04341.x>.
- Zuardi AW, Crippa JA, Hallak JE, Moreira FA, Guimarães FS. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. *Braz J Med Biol Res* 2006 Apr;39(4):421-9. DOI: <http://dx.doi.org/10.1590/s0100-879x2006000400001>.
- Fingerle J. CB2 agonism protects from inflammation related kidney damage and fibrosis. *Proceedings of the 25th Anniversary Symposium of the International Cannabinoid Research Society*; 2015 Jun 28-Jul 3; Wolfville, Nova Scotia, Canada.
- Purohit V. Role of cannabinoids in chronic pain. *Proceedings of the 25th Anniversary Symposium of the International Cannabinoid Research Society*; 2015 Jun 28-Jul 3; Wolfville, Nova Scotia, Canada.
- Starowicz K. Role of endocannabinoid system in pathogenesis of osteoarthritic pain. *Proceedings of the 25th Anniversary Symposium of the International Cannabinoid Research Society*; 2015 Jun 28-Jul 3; Wolfville, Nova Scotia, Canada.
- Liu A. Therapeutic efficacy of a peripherally restricted CB1R antagonist/AMPK activator in diet-induced obesity/metabolic syndrome. *Proceedings of the 25th Anniversary Symposium of the International Cannabinoid Research Society*; 2015 Jun 28-Jul 3; Wolfville, Nova Scotia, Canada.
- Bergamaschi MM, Queiroz RH, Zuardi AW, Crippa JA. Safety and side effects of cannabidiol, a Cannabis sativa constituent. *Curr Drug Saf* 2011 Sep 1;6(4):237-49. DOI: <http://dx.doi.org/10.2174/157488611798280924>.
- Ferreira VR, Carvalho LB, Ruotolo F, de Morais JF, Prado LB, Prado GF. Sleep disturbance scale for children: translation, cultural adaptation, and validation. *Sleep Med* 2009 Apr;10(4):457-63. DOI: <http://dx.doi.org/10.1016/j.sleep.2008.03.018>.
- Birmaher B, Khetarpal S, Cully M, Brent D, McKenzie S. Screen for child anxiety related disorders (SCARED) [Internet]. Pittsburgh, PA: Western Psychiatric Institute and Clinic, University of Pittsburgh; 1995 Oct [cited 2016 Apr 26]. Available from: www.pediatricbipolar.pitt.edu/content.asp?id=2333#3304.
- Pace-Schott EF, Germain A, Milad MR. Sleep and REM sleep disturbance in the pathophysiology of PTSD: the role of extinction memory. *Biol Mood Anxiety Disord* 2015 May 29;5:3. DOI: <http://dx.doi.org/10.1186/s13587-015-0018-9>.
- Hsiao YT, Yi PL, Li CL, Chang FC. Effect of cannabidiol on sleep disruption induced by the repeated combination tests consisting of open field and elevated plus-maze in rats. *Neuropharmacology* 2012 Jan;62(1):373-84. DOI: <http://dx.doi.org/10.1016/j.neuropharm.2011.08.013>.

Marijuana and Medicine

Scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily [tetrahydrocannabinol], for pain relief, control of nausea and vomiting, and appetite stimulation; smoked marijuana, however, is a crude [tetrahydrocannabinol] delivery system that also delivers harmful substances.

— Joy JE, Watson SJ Jr, Benson JA Jr. *Marijuana and medicine: Assessing the science base*. Washington, DC: National Academies Press; 1999.



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Research paper

Cannabis for therapeutic purposes: Patient characteristics, access, and reasons for use

Zach Walsh^{a,*}, Robert Callaway^b, Lynne Belle-Isle^{c,d}, Rielle Capler^e, Robert Kay^f, Philippe Lucas^d, Susan Holtzman^a

^a University of British Columbia, 3333 University Way, Kelowna, BC V1V1V7, Canada

^b 1814B Edgehill Court, Kelowna, BC V1V 1R7, Canada

^c Canadian AIDS Society, 190 O'Connor Street, Suite 100, Ottawa, ON K2P2R3, Canada

^d Centre for Addictions Research of British Columbia, PO Box 1700 STN CSC, Victoria, BC V8W 2Y2, Canada

^e Canadian Association of Medical Cannabis Dispensaries, Box 14, Lions Bay, BC V0N 2E0, Canada

^f Green Cannapy Research and Development, 288 Highway 33W, Kelowna, BC V1X 1X7, Canada

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ABSTRACT

Background: The authorized and unauthorized use of cannabis for therapeutic purposes (CTP) has increased dramatically in recent years, and physicians have called for further research to better clarify the parameters of effective and appropriate use. We report findings from a large cross-sectional study of the use of CTP in Canada and compare use across medical conditions and across authorized and unauthorized users.

Methods: We examined cannabis use history, medical conditions and symptoms, patterns of current use of CTP, modes of access and perceived effectiveness among 628 self-selected Canadians consumers of CTP. Participants were recruited from medical cannabis dispensaries and from organizations that assist users of CTP.

Results: Patients reported using cannabis to treat multiple symptoms, with sleep, pain, and anxiety being the most common. Cannabis was perceived to provide effective symptoms relief across medical conditions. Patterns of use were also consistent across medical conditions. Notable differences were observed with regard to modes of access.

Conclusion: Across medical conditions respondents reported using cannabis to effectively address diverse symptoms. Results indicate a substantial disconnect between the therapeutic use of cannabis and research on the risks and benefits of such use; particularly with regard to the anxiolytic and sedative use of cannabis. Authorized and unauthorized users exhibited few meaningful differences with regard to medical conditions and patterns of use, but faced substantial differences regarding access.

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Cannabis has a long history of medical use (Abel, 1980; Earleywine, 2005; Iverson, 2008), and after decades of marginalization the therapeutic properties of cannabis and cannabis derivatives are receiving increased attention (Earleywine, 2005; Holland, 2010; Lucas, 2008). Indeed, robust and growing evidence indicates that cannabis has medical benefits for diverse conditions and an acceptable risk profile (Joy, Watson, & Benson, 2003). In response to legal recognition of the constitutional rights of Canadians to access cannabis for therapeutic purposes (CTP), the federal government enacted the *Marihuana Medical Access Regulations* and

initiated a centralized program in 2001, and in 2003 Health Canada began to provide CTP to patients. This program authorizes two categories of individuals to possess cannabis for medical purposes; Category 1 includes symptoms associated with HIV/AIDS, arthritis, spinal cord injury or disease, cancer, epilepsy, or MS, whereas Category 2 includes other symptoms and conditions assessed by a physician and a specialist. Those authorized can purchase dried cannabis from Health Canada, can purchase seeds to grow cannabis, or designate a person to grow cannabis on their behalf. In addition, medical cannabis dispensaries that operate under an ambiguous legal status provide CTP and related services to over 50,000 patients across Canada (Lucas, 2008).

Despite widespread concern with the efficiency of the Health Canada program (Holland, 2010), registration has grown exponentially from under 500 registrants in 2002 to over 26,000 in 2012 (Health Canada, 2012a). National surveys indicate substantial access outside of the Health Canada program; recent estimates

* Corresponding author. Tel.: +1 250 807 9373.

E-mail addresses: zachary.walsh@ubc.ca (Z. Walsh), rojocal@yahoo.ca (R. Callaway), LynneB@cdnaids.ca (L. Belle-Isle), rielle@telus.net (R. Capler), bekindok@hotmail.com (R. Kay), plucas@uvic.ca (P. Lucas), susan.holtzman@ubc.ca (S. Holtzman).

suggest that 400,000 to 1,000,000 Canadians use CTP (Health Canada, 2011). Diverse reasons for use and multiple modes of access complicate the characterization of use of CTP, and health care professionals have expressed concern regarding the dearth of information on CTP; a recent Canadian Medical Association-sponsored survey reported that over 80% of physicians wanted more information on therapeutic indications, clinical guidelines, and risks and benefits of CTP (CMA, 2012).

Several studies have examined CTP use among Canadians. A regional survey reported that approximately 2% of adults used CTP in the past year, primarily to relieve nausea and pain (Braitstein et al., 2001), and a more recent national survey estimated that one million Canadians, or 4% of those aged 15 and older, used cannabis to treat self-defined medical conditions in the previous 12 months (Adlaf, Begin, & Sawka, 2005). Studies of persons living with HIV/AIDS report rates of 15–30% use of CTP, primarily for treatment of nausea, pain, and mood-related symptoms (Belle-Isle & Hathaway, 2007; Ware, Rueda, Singer, & Kilby, 2003). Studies of patients with MS and patients with chronic pain report similar results; approximately 15% of respondents report use of CTP with high levels of perceived effectiveness for diverse symptoms including nausea, pain, and mood (Belle-Isle & Hathaway, 2007; Ware et al., 2003; Clark, Ware, Yazer, Murray, & Lynch, 2004). Studies of CTP from the US, Europe, and Australia report findings that are consistent with those of Canadian studies; CTP is perceived to be an effective treatment for symptoms including pain, nausea, and negative mood (Grotenherman & Schnelle, 2003; Harris et al., 2000; Lucas, 2012; Reiman, 2007; Reinerman, Nunberg, Lanthier, & Heddleston, 2011; Swift, Gates, & Dillon, 2005; Ware, Adams, & Guy, 2005).

In sum, patient-centered research provides evidence for the acceptability and perceived effectiveness of CTP. However, substantial knowledge gaps remain and health care professionals have explicitly called for further research to better specify the parameters for appropriate use of CTP (CMA, 2012). Indeed, to date no studies have directly compared use of CTP across medical conditions or across modes of access (i.e., authorized vs. unauthorized). In the present study we report demographic characteristics, medical conditions and symptoms, reasons for use, perceived effects, and authorized and unauthorized modes of accessing CTP among Canadians. Comparing users of CTP across symptoms and across medical conditions with regard to patterns of use, and perceived effectiveness may help direct future controlled studies of the efficacy of CTP for specific conditions, and inform the development of tailored CTP regimens. In addition, comparing authorized and unauthorized CTP users may elucidate factors that underlie patient adoption of the Canadian CTP program, and help to guide the refinement of the complex process of CTP distribution and monitoring.

Method

Design

We obtained cross-sectional data in 2011–2012 from 628 self-selected current CTP users. Participants were recruited from two contexts; *national* participants completed the survey online from the location of their choice, and *local* participants completed the survey at a cannabis dispensary in the Interior region of British Columbia (BC). This recruitment strategy was designed to allow for comparison of the relatively less controlled online *national* condition with the confirmed CTP users queried in-person in the *local* condition. A total of 702 *national* participants completed the consent form, of whom 541 (77%) reported current CTP use. All 87 *local* participants who completed the consent form reported current CTP use. The *national* survey was promoted via organizations and media

Table 1
Demographics.

	CTP patients, % (n)	Census, %	Z
Male	71(443)	49	11.03 ^a
Ethnicity			
White	92 (581)	80	7.52 ^a
Aboriginal	7 (47)	4	3.80 ^a
Age			
18–24yrs old	17 (99)	12	3.86 ^a
25–34	26 (158)	16	6.84 ^a
35–44	19 (115)	20	.63
45–54	24 (141)	20	2.51
55>	14 (85)	32	9.67 ^a
Education			
<high School	4 (27)	15	-7.86 ^a
HS Grad	37(234)	24	7.63 ^a
% post secondary	58 (367)	61	-1.54
Income			
<\$20,000	33 (206)	44	-5.55 ^a
\$20,000–39,999	26 (165)	27	-.56
\$40,000–59,999	17 (103)	15	1.43
\$60,00 +	24 (146)	14	7.22 ^a
Residence			
Rural	22 (137)	20	1.25
Urban	78 (485)	80	-1.25

Note: Z = One sample Z-test for proportions, comparing medical cannabis users to values from the 2006 Canadian Census (Statistics Canada, 2006).

^a $p < .01$.

that serve users of CTP patients (e.g., Canadian AIDS Society, Canadian Aboriginal AIDS Network, Cannabis Culture), and by national advertisements at MC dispensaries. To preserve confidentiality, no identifying data (i.e. IP addresses) were collected for *national* participants. The *local* group was comprised of dispensary members who were either authorized to possess cannabis through Health Canada or had documented confirmation of a medical condition for which CTP is indicated. No confirmation of medical condition was provided for *national* participants; however such confirmation is required to obtain Health Canada authorization and to obtain dispensary membership. Participants in the *local* group were compensated \$10 and were aided by research assistants; participants in the *national* group were not assisted or financially compensated.

The survey was designed to be completed in less than one hour, and consisted of a total of 414 adaptive questions administered online without forced response. The survey was organized hierarchically such that many items were contingent on prior responses; as a result, respondents were presented with diverse item sets and response rates for specific items, and total response times varied accordingly. The survey was developed based on previous research, and on consultations with a community research board comprised of CTP patients and experts, and includes questions drawn from a prior study of CTP use (Belle-Isle & Hathaway, 2007). It queried access, perceived effectiveness, patterns and history of cannabis use, medical diagnoses and symptoms, mood, and demographics (a copy of the survey is available upon request from the first author). The study was approved by the Behavioural Research Ethics Board of the Okanagan campus of the University of British Columbia. All categorical data were compared using χ^2 . In light of varying response rates across items, total number of responses is reported for each analysis. Due to the large number of comparisons all significance testing was conducted at the $p < .01$ level to minimize the likelihood of interpreting chance results while maintaining power (Nakagawa, 2004).

Results

Preliminary analyses

We compared the responses of *local* participants who reported residency in the province of BC and accessing CTP via

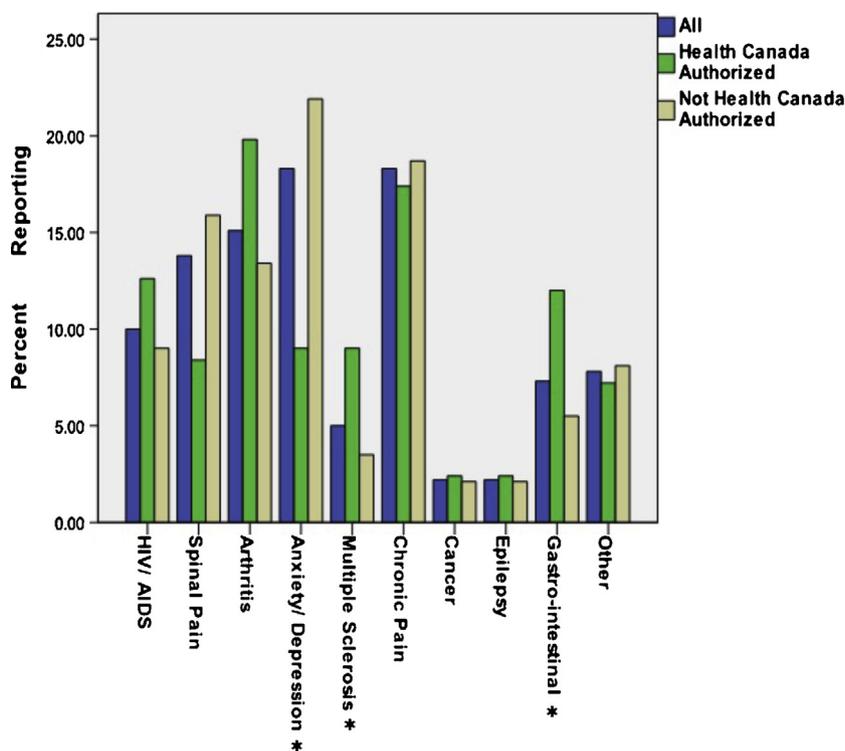


Fig. 1. Primary medical conditions treated with cannabis by authorization. *Note:* Sleep Disorders, Attention Deficit Disorder, Fibromyalgia, Hepatitis C, Parkinson’s Disease, Wilson’s Disease, Scleroderma, Tourette’s Syndrome, and unspecified Psychotic Disorder Conditions each comprised less than 2% of the sample and were aggregated into the category ‘Other’. The anxiety and mood disorders category included 35 participants who reported a primary *illness/condition* of anxiety, 34 who reported depression and 40 who reported both anxiety and depression. Comparisons of these groups indicated equivalent profiles with regard to demographic characteristics, health, and use of CTP, and were therefore aggregated for statistical analyses; $n = 502$ * = difference between proportion Health Canada Authorized and Unauthorized $p < .01$.

dispensary ($n = 63$) to *national* participants who reported BC residency and accessing CTP via dispensary ($n = 53$). Analysis indicated no differences with regard to quantity or frequency of cannabis use, and indicated substantial similarity with regard to primary medical condition; the only difference was a smaller proportion of *local* respondents reporting gastrointestinal (GI) condition as primary ($\chi^2 = 8.94 (1), p < .01$). This broad similarity between in-person confirmed users of CTP (i.e. *local*) and online respondents increased our confidence in the validity of online responses.

Demographics

Comparisons of the sample to values drawn from the Canadian 2006 Census of Population (Statistics Canada, 2006; Table 1) indicated that male, White, and Aboriginal participants were over-represented. The users of CTP were also younger, had a higher income, and were more likely to have completed high school. The regional distribution was consistent with participation in the Health Canada program (Health Canada, 2012b).

Medical conditions and symptoms

Participants were queried regarding a single primary *condition* treated with cannabis (Fig. 1). Participants also checked all applicable *symptoms* (Table 2) they treated with cannabis from a list. The mean number of symptoms patients endorsed treating was 6.74 ($n = 605$, $SD = 3.00$, Median = 6.00, Interquartile range = 4.00–8.00). Symptoms reportedly treated with CTP by fewer than 10% of the sample include high blood pressure (9%), tics (8%), regulating blood sugar (7%), seizures (6%), bladder dyscontrol (6%) and impotence (6%). Aggregate examination across *condition* indicated that pain, anxiety, and sleep problems were the most frequently endorsed

symptoms; 57% reported use to address all three symptoms, and 99% endorsed treating one or more of the three.

Symptoms treated with cannabis varied across *condition* (Table 2). Use to address pain symptoms was more prevalent among individuals whose primary conditions were pain-related (i.e., chronic spinal and non-spinal pain, arthritis). Chronic spinal pain participants were more likely to report treating muscle spasms. Participants with arthritis were more likely to report use for inflammation and ocular pressure, and less likely to report use to address anxiety and appetite. Participants who identified mood and anxiety disorders as their primary condition were more likely to use cannabis to address mental health-related symptoms (i.e., anxiety, depression, aggression, mania/psychosis), and were less likely to treat pain, inflammation, and muscle spasms. Participants who identified HIV/AIDS or GI as their primary conditions were more likely to treat symptoms of nausea and appetite, and HIV/AIDS was associated with less treatment of pain and aggression. Overall, cannabis was perceived to provide effective symptoms relief; 72% ($n = 439$) reported that CTP was *always* helpful and an additional 24% ($n = 147$) described it as *often* helpful. The proportion of participants who described CTP as *always* helpful was relatively consistent across conditions. The only difference across groups was relatively lower endorsement of *always* helpful (55%) by participants with HIV/AIDS ($\chi^2 = 10.04 (1), n = 593, p < .01$). Over half (57%, $n = 358$) of participants reported using other medications to address the symptoms they were treating with CTP. Of these, 79% ($n = 281$) described CTP as having fewer side effects than the concurrent treatment.

Use patterns

History of non-therapeutic cannabis use prior to therapeutic use was reported by 82% ($n = 441$) of participants.

Table 2
 Symptoms addressed with medical cannabis by condition.

	All		Pain-spinal			Pain–nonspinal			Arthritis			Mood			HIV/AIDS			GI		
	n	%	n	%	X ²	n	%	X ²	n	%	X ²	n	%	X ²	n	%	X ²	n	%	X ²
Sleep	502	85	68	83	0.35	93	85	<.01	80	90	1.91	99	93	5.7	47	78	2.4	33	77	2.54
Pain	486	82	80	98	15.13 ^a	102	94	11.56 ^a	86	97	14.67 ^a	56	52	81.21 ^a	41	68	9.07 ^a	40	93	3.62
Anxiety	463	79	65	79	0.04	85	78	0.02	57	64	12.92 ^a	106	99	32.81 ^a	44	73	1.05	29	67	3.34
Depression	394	67	55	67	<.01	68	62	1.16	51	57	4.24	98	92	36.26*	34	57	3.08	27	63	0.33
Appetite/weight	331	56	43	52	0.52	56	51	1.21	35	39	11.98 ^a	61	57	0.04	46	77	11.47 ^a	33	77	8.02 ^a
Nausea	294	49	36	44	1.34	56	51	0.13	33	37	6.82 ^a	43	40	4.86	47	78	21.71 ^a	35	81	18.48 ^a
Inflammation	291	49	51	62	6.31	52	48	0.14	79	89	65.23 ^a	25	23	35.23 ^a	20	33	6.83 ^a	25	58	1.44
Spasms	280	48	58	71	20.69 ^a	53	49	0.07	50	56	3.2	23	22	35.33 ^a	20	33	5.34	22	51	0.255
Headache	237	40	44	54	7.21	56	51	6.99 ^a	36	40	<.01	38	36	1.18	15	25	6.4	12	28	2.9
Aggression	140	24	19	23	0.01	28	26	0.28	16	18	1.92	42	39	17.40 ^a	5	8	8.75 ^a	8	19	0.67
Drug Withdrawal	76	13	10	12	0.04	17	16	0.88	10	11	0.25	18	17	1.81	8	13	0.01	1	2	4.61
Ocular Pressure	68	12	11	13	0.33	11	10	0.27	19	21	9.92 ^a	8	8	2.1	7	12	<.01	1	2	3.85
Mania/Psychosis	67	11	9	11	0.01	11	10	0.21	7	8	1.27	25	23	18.72 ^a	4	7	1.46	5	12	<.01
Respiratory	67	11	5	6	2.62	20	18	6.5	14	16	1.99	12	11	<.01	3	5	2.68	6	14	0.31
Skin Conditions	63	11	8	10	0.08	7	6	2.54	13	15	1.7	16	15	2.51	3	5	2.26	5	12	0.04

Note: X² = Comparison of each groups versus aggregation of other groups.

^a p < .01.

Mean age was 17.30 years ($n=540$, $SD=7.08$, Median = 16, Interquartile range = 14.00–18.00) for first use and 28.35 years ($n=538$, $SD=11.25$, Median = 25, Interquartile range = 19.00–37.00) for first therapeutic use. Individuals with and without history of non-therapeutic use did not differ with regard to demographic characteristics, or conditions and symptoms. Most participants who reported prior use reported increased use with the initiation of therapeutic use; 33% reported a large increase and 32% a small increase, whereas 7% reported a large decrease and 10% a small decrease. Aggregate analyses indicated that 40% ($n=167$) of users fell into the modal quantity of use category of *more than 14 grams per week*, and that 42% ($n=226$) fell in the modal frequency of use group reporting *2–3 uses per day*. Among the group that used more than 14 grams per week, the median weekly amount used was 28 grams (Interquartile range = 21–45). Comparisons of the six medical conditions that each account for 5% or more of the sample (Table 3) indicated no difference with regard to modes of use and few differences in patterns of use; a larger proportion of individuals identifying HIV/AIDS as primary condition were among the groups with lowest quantity and frequency of use, and those who identified anxiety and/or depression as primary conditions were less likely to fall in the most frequent use group. Overall health quality was also associated with frequency of use such that participants who described their overall health as *fair* or

poor (34%, $n=161$) were overrepresented in the most frequent use group ($X^2=8.31$ (1), $n=473$, $p<.01$).

Access

Aggregate examination indicated that 32% ($n=167$) of respondents had Health Canada authorization to possess CTP. An additional 12% ($n=64$) had applications in process, and 3% ($n=13$) had applied and been rejected. The proportion of authorized individuals varied across condition (Fig. 1); individuals who identified anxiety and/or depression as primary condition were less likely to be authorized ($X^2=13.13$ (1), $n=502$, $p<.01$), whereas a greater proportion of MS ($X^2=11.08$ (1), $n=502$, $p<.01$) and GI ($X^2=8.68$ (1), $n=502$, $p<.01$) participants were authorized. Most participants reported using more than one mode of accessing CTP; the mean number of access modalities was 1.89 ($n=500$, $SD=.88$, Median = 2.00, Interquartile range = 1.00–2.00). Authorization was a determinant of access (Fig. 2); the mean number of access modalities for authorized individuals was 2.11 ($n=162$, $SD=.98$, Median = 2.00, Interquartile range = 1.00–3.00) compared to 1.78 ($n=337$, $SD=.81$, Median = 2.00, Interquartile range = 1.00–2.00) for unauthorized users ($F(1, 497)=16.26$, $p<.01$). Authorized users were more likely to access CTP via Health Canada ($X^2=11.88$ (1), $n=443$, $p<.01$), to grow for themselves ($X^2=31.42$ (1), $n=493$,

Table 3
 Characteristics of cannabis use by condition.

	All		Pain-spinal			Pain–nonspinal			Arthritis			Mood			HIV/AIDS			GI		
	n	%	n	%	X ²	n	%	X ²	n	%	X ²	n	%	X ²	n	%	X ²	n	%	X ²
Amount per week (Grams)																				
≤2	42	9	5	8	0.1	9	10	0.13	3	4	2.59	9	10	0.3	11	27	18.01 ^a	1	3	1.68
2.1–5	60	13	8	13	<.01	11	12	0.05	10	13	0.04	11	13	<.01	5	12	<.01	0	0	5.46
5.1–9	85	18	7	11	2.44	22	24	2.81	11	15	0.63	24	28	6.81 ^a	6	15	0.33	6	17	0.02
9.1–14	76	16	15	24	3.04	15	16	<.01	15	20	1.06	11	13	0.89	4	10	1.3	6	17	0.04
>14	212	45	29	45	0.01	35	38	2	46	48	0.41	32	37	2.66	15	37	1.18	22	63	5.08
Frequency of use																				
< daily	58	11	6	9	0.4	13	13	0.31	3	4	4.72	13	14	1.06	13	25	10.85 ^a	2	5	1.4
1x day	71	14	7	10	0.71	16	16	0.43	12	16	0.32	17	19	2.31	8	15	0.12	1	3	4.17
2–3x	174	33	21	31	0.19	31	30	0.56	26	34	0.01	36	39	1.77	16	30	0.24	14	37	0.24
4x+	221	42	34	50	1.96	43	42	0.01	36	47	0.78	26	28	8.86 ^a	16	30	3.48	21	55	2.88
Preferred mode of use																				
Smoke ($n=513$)	293	57	35	54	0.33	62	61	0.94	41	53	0.55	48	53	0.86	35	67	2.45	24	65	0.98
Vaporize ($n=502$)	217	43	31	49	1.05	42	43	<.01	30	39	0.67	37	41	0.3	22	44	0.01	16	43	<.01
Oral ($n=501$)	139	28	16	26	0.13	29	30	0.21	29	39	5.25	25	26	0.1	15	31	0.22	8	22	0.75

Note: X² = Comparison of each groups versus aggregation of other groups.

^a p < .01.

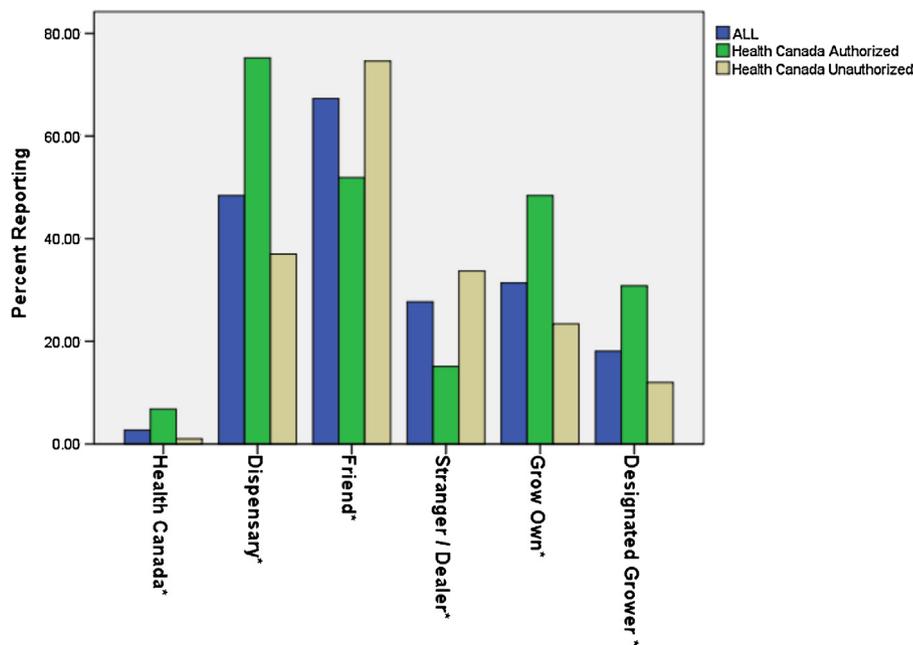


Fig. 2. Modes of Access. Note: * = difference between proportion Health Canada Authorized and Unauthorized $p < .01$; $n = 498$.

$p < .01$), have a designate grow for them ($X^2 = 25.85$ (1), $n = 493$, $p < .01$) or use a dispensary ($X^2 = 54.46$ (1), $n = 444$, $p < .01$). In contrast, unauthorized users were more likely to access CTP from a friend ($X^2 = 25.46$ (1), $n = 495$, $p < .01$) or from a stranger ($X^2 = 18.69$ (1), $n = 494$, $p < .01$).

Discussion

Canadians use cannabis to treat diverse conditions and symptoms in a manner that only partially overlaps with the federally authorized program. There is considerable consistency with regard to patterns of use and reported effectiveness; nearly all respondents used cannabis to treat pain, anxiety, or sleep disturbances, and over half used it to treat all three symptoms. We also observed consistency across participants with and without histories of non-therapeutic cannabis use, which suggests that, with regard to CTP, individuals who may enjoy non-therapeutic use of cannabis were not different with regard to therapeutic application of cannabis from those participants who may have been less likely to expect extra-therapeutic benefit. The substantial minority of respondents who were federally authorized to possess cannabis exhibited few differences from unauthorized users with regard to symptoms treated and patterns of use, but differed considerably with regard to mode of access.

Most respondents reported using CTP to treat conditions that are explicitly listed within the federal program; however, a large contingent also reported use for other conditions. Comparisons of symptoms treated across conditions indicated high levels of congruence (e.g., respondents with pain-related conditions were more likely to use cannabis to address pain symptoms), but also reflected substantial consistency across conditions. Specifically, use to treat sleep disturbances, and to a lesser extent anxiety and depression, was consistently high across conditions. However, despite widespread use for anxiolytic and sedative purposes, participants who reported anxiety or depression as primary reason for CTP use were less likely to have obtained federal authorization to access CTP. This may be due to the absence of these conditions among those explicitly listed by the federal program, but may also reflect accentuated stigma associated with the use of cannabis to address mental health issues. Indeed, stigma has been identified as a

substantial barrier to accessing care for mental health conditions such as depression and anxiety (Brown et al., 2010), and this may be compounded by the considerable stigma associated with use of CTP (Bottorff et al., 2013) to create a substantial barrier to accessing treatment. Research that further elucidates the appropriateness of using cannabis to treat anxiety and depression is required to guide effective treatment and help to reduce stigma.

Patterns of use were also consistent across medical conditions, with the only notable difference being slightly lower levels of use among respondents with HIV/AIDS, a difference which may be due to intermittent use to address nausea. Most participants reported initiating non-therapeutic use prior to use of CTP, and noted increased levels of use associated with the transition to therapeutic use. This reported increase is consistent with our observation that the median level of therapeutic use exceeds typical levels of non-therapeutic use (Reinarman, Cohen, & Kaal, 2004; Hazekamp et al., 2013; but see also Hazekamp & Heerdink, 2013), and suggests a potentially meaningful distinction between therapeutic and non-therapeutic use. In contrast, the relative consistency of use among CTP-users suggests that CTP regimens might transfer well across conditions, and enjoy good adherence. The most pronounced differences across respondents involved modes of access, such that unauthorized users were much less likely to access CTP from authorized, or semi-authorized (i.e. dispensaries) sources. This discrepancy contrasts with the pronounced similarity between authorized and unauthorized users on indicators of health and use of CTP, and suggests that the current system of authorization may not be discriminating among qualitatively different groups.

The primary limitations of this study are common to online medical surveys such as potential for multiple responses from a single respondent, a potentially unrepresentative sample, and lack of physician confirmation of medical conditions. In addition, response bias related to participant self-selection, and recruitment through organizations that support medical cannabis patients likely resulted in overrepresentation in our sample by individuals who respond favourably to CTP. In light of this potential bias, our characterization of the therapeutic use of cannabis should be interpreted with caution pending replication from research that employs a more systematic recruitment approach. However, these limitations are counterbalanced by several methodological

strengths including the inclusion of an in-person subsample, engagement of a community research board in the development and dissemination of the survey, and general adherence to established standards for reporting internet-based surveys (Eysenbach, 2004).

Conclusions

This was the largest and most comprehensive study to date of the therapeutic use of cannabis in Canada. We draw three primary conclusions from the data. First, reasons for use and perceived effectiveness were generally consistent across medical conditions; respondents overwhelmingly reported using cannabis to effectively address pain, sleep disturbance, and anxiety. Second, further research is required to address the substantial disconnect between the therapeutic use of cannabis and research on the risks and benefits of such use. This is particularly evident with regard to the anxiolytic and sedative use of cannabis; extrapolation from our sample to the national population of CTP users suggests levels of use for anxiolytic and sedative purposes that may be comparable to the number of Canadians who currently use benzodiazepine and other sedatives (Kassam & Patten, 2006). Such widespread use suggests a need for the systematic evaluation of the effectiveness and adverse effects of cannabis for the treatment of these conditions, as well as comparisons of cannabis with the widely-used pharmaceutical products that currently represent frontline treatments. Finally, our findings highlight the apparent discrepancy in access to cannabis across CTP users. Authorized and unauthorized users exhibit few meaningful differences with regard to medical conditions and patterns of use, but face substantial differences regarding access; many seriously ill Canadians risk increased stigma (Bottorf, Bissell, Balneaves, Oliffe, Capler & Buxton, 2013), legal sanction, and other negative outcomes associated with accessing cannabis from illegal markets. At the time of this writing the federal medical cannabis program is undergoing substantial structural changes. The present study provides a baseline for assessing the impact of these changes, the most important of which must surely involve providing a program that facilitates informed, safe, legal, and affordable access to a source of CTP for ill Canadians.

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Conflict of interest statement

None of the authors have any conflicts of interest with regard to the contents of this manuscript. Access.

References

- Abel, E. L. (1980). *Marijuana: The first twelve thousand years*. New York: Plenum Press.
- Adlaf, E. M., Begin, P., & Sawka, E. (2005). *Canadian Addiction Survey (CAS): A national survey of Canadian's use of alcohol and other drugs: Prevalence of use and related harms: Detailed report*. Ottawa: Canadian Centre on Substance Use.
- Belle-Isle, L., & Hathaway, A. (2007). Barriers to access to medical cannabis for Canadians living with HIV/AIDS. *AIDS Care*, 19, 500–506. <http://dx.doi.org/10.1080/09540120701207833>
- Bottorf, J. L., Bissell, L. J., Balneaves, L. G., Oliffe, J. L., Capler, N. R., & Buxton, J. (2013). Perceptions of cannabis as a stigmatized medicine: a qualitative descriptive study. *Harm Reduction Journal*, 10, 1–10. <http://dx.doi.org/10.1186/1477-7517-10-2>
- Braitstein, P., Kendall, T., Chan, K., Wood, E., Montaner, J. S., O'Shaughnessy, M. V., & Hogg, R. S. (2001). Mary-Jane and her patients: Sociodemographic and clinical characteristics of HIV-positive individuals using medical marijuana and antiretroviral agents. *AIDS*, 15, 532–533.
- Brown, C., Conner, K., Copeland, V. C., Grote, N., Beach, S., Battista, D., & Reynolds, C. F. (2010). Depression stigma, race, and treatment seeking behavior and attitudes. *Journal of Community Psychology*, 38, 350–368.
- Canadian Medical Association. (2012). *Our members' views on medicinal marijuana*. Retrieved from <http://www.cma.ca/advocacy/epanel-medicinal-marijuana>.
- Clark, A. J., Ware, M. A., Yzer, E., Murray, T. J., & Lynch, M. E. (2004). Patterns of cannabis use among patients with multiple sclerosis. *Neurology*, 62, 2098–2100.
- Earleywine, M. (2005). *Understanding marijuana: A new look at the scientific evidence*. New York: Oxford University Press.
- Eysenbach, G. (2004). Improving the quality of web surveys: The checklist for reporting the results of internet e-surveys. *Journal of Medical Internet Research*, 3, e34. <http://dx.doi.org/10.2196/jmir.6.3.e34>
- Grotenherman, F., & Schnelle, M. (2003). Survey on the medical use of cannabis and THC in Germany. *Journal of Cannabis Therapeutics*, 3(2), 17–40. http://dx.doi.org/10.1300/J175v03n02_03
- Harris, D., Jones, R. T., Shank, R., Nath, R., Fernandez, E., Goldstein, K., & Mendelson, J. (2000). Self-reported marijuana effects and characteristics of 100 San Francisco medical marijuana club members. *Journal of Addictive Diseases*, 19(3), 89–103. http://dx.doi.org/10.1300/J069v19n03_07
- Hazekamp, A., & Heerdink, E. (2013). The prevalence and incidence of medicinal cannabis on prescription in The Netherlands. *European Journal of Clinical Pharmacology*, 69, 1575–1580. <http://dx.doi.org/10.1007/s00228-013-1503-y>
- Hazekamp, A., Mueller-Vahl, K., Ware, M., et al. (2013). The medicinal use of cannabis and cannabinoids; an international cross-sectional survey on methods of intake. *Journal of Psychoactive Drugs*, in press.
- Health Canada. (2011). *Canadian Alcohol and Drug Use Monitoring Survey (CADUMS)*. Retrieved from <http://www.hc-sc.gc.ca/hc-ps/drugs-drogues/stat/2011/summary-sommaire-eng.php>.
- Health Canada. (2012 (December 26)). *Harper government announces new marijuana for medical purposes regulations: Changes improve public safety maintain patient access*. Retrieved from <http://www.hc-sc.gc.ca/ahc-asc/media/nrcp/2012/2012-193-eng.php>.
- Health Canada. (2012). *Marijuana medical access program statistics*. Retrieved from: <http://www.hc-sc.gc.ca/dhp-mps/marihuana/stat/index-eng.php#a1>.
- Holland, J. (2010). *The pot book: A complete guide to cannabis: Its role in medicine, politics, science, and culture*. Toronto: Park Street Press.
- Iverson, L. L. (2008). *The science of marijuana* (2nd ed.). Oxford, UK: Oxford University Press.
- Joy, J., Watson, S., & Benson, J. (2003). *Marijuana and medicine*. Institute of Medicine: National Academy Press.
- Kassam, A., & Patten, S. B. (2006). Major depression, fibromyalgia and labour force participation: A population-based cross-sectional study. *BMC Musculoskeletal Disorders*, 7, 4. <http://dx.doi.org/10.1186/1471-2474-7-4>
- Lucas, P. (2008). Regulating compassion: An overview of Canada's federal medical cannabis policy and practice. *Harm Reduction Journal*, 5, 5. <http://dx.doi.org/10.1186/1477-7517-5-5>
- Lucas, P. (2012). It can't hurt to ask: A patient-centered quality of service assessment of Health Canada's medical cannabis policy and program. *Harm Reduction Journal*, 9(2) <http://dx.doi.org/10.1186/1477-7517-9-2>
- Nakagawa, S. (2004). A farewell to Bonferroni: The problems of low statistical power and publication bias. *Behavioral Ecology*, 15(6), 1044–1045.
- Reiman, A. (2007). Medical cannabis patients: Patient profiles and health care utilization patterns. *Complementary Health Practice Review*, 12, 31–50. <http://dx.doi.org/10.1177/1533210107301834>
- Reinarman, C., Cohen, P. D. A., & Kaal, H. L. (2004). The limited relevance of drug policy: Cannabis in Amsterdam and in San Francisco. *American Journal of Public Health*, 94, 836–842. <http://dx.doi.org/10.2105/AJPH.94.5.836>
- Reinarman, C., Nunberg, H., Lanthier, F., & Heddleston, T. (2011). Who are medical marijuana patients? Population characteristics from nine California assessment clinics. *Journal of Psychoactive Drugs*, 43, 128–135. <http://dx.doi.org/10.1080/02791072.2011.587700>
- Statistics Canada. (2006). *2006 census of population*. Retrieved from <http://www12.statcan.gc.ca/census-recensement/2006/index-eng.cfm>.
- Swift, W., Gates, P., & Dillon, P. (2005). Survey of Australians using cannabis for medical purposes. *Harm Reduction Journal*, 2, 18–27. <http://dx.doi.org/10.1186/1477-7517-2-18>
- Ware, M. A., Adams, H., & Guy, G. W. (2005). The medicinal use of cannabis in the UK: Results of a nationwide survey. *International Journal of Clinical Practice*, 59, 291–295. <http://dx.doi.org/10.1111/j.1368-5031.2005.00271.x>
- Ware, M. A., Rueda, S., Singer, J., & Kilby, D. (2003). Cannabis use by persons living with HIV/AIDS: Patterns and prevalence of use. *Journal of Cannabis Therapeutics*, 3(2), 3–15. http://dx.doi.org/10.1300/J175v03n02_02

Is the medical use of cannabis a therapeutic option for children?

Michael J Rieder; Canadian Paediatric Society, Drug Therapy and Hazardous Substances Committee



Français en page 35

MJ Rieder, Canadian Paediatric Society, Drug Therapy and Hazardous Substances Committee. Is the medical use of cannabis a therapeutic option for children? *Paediatr Child Health* 2016;21(1):31-38.

Cannabis is a psychoactive compound with a long history of recreational and therapeutic use. Current considerations regarding cannabis use for medical purposes in children have been stimulated by recent case reports describing its beneficial effect with refractory epilepsy. Overall, there are insufficient data to support either the efficacy or safety of cannabis use for any indications in children, and an increasing body of data suggests possible harm, most importantly in specific conditions. The potential for cannabis as a therapeutic agent must be evaluated carefully for both efficacy and safety in treating specific paediatric health conditions. Smoking is not an acceptable mode of drug delivery for children. The use of cannabis for medical purposes in specific cases should not be construed as a justification for recreational cannabis use by adolescents. Recommendations for therapeutic use in exceptional paediatric cases are offered, always providing that this treatment course is carefully evaluated in individuals and in ongoing, well-designed research studies to determine safety and efficacy.

Key Words: *Cannabinoids; Children; Epilepsy; Medical marijuana; Nabiximols; Smoking*

Marijuana is a psychoactive substance prepared from the dried flowers and subtending leaves and stems of the female cannabis plant, usually *Cannabis sativa*, which is most commonly consumed by inhalation from smoking.(1) In contrast, cannabis refers to the various psychoactive preparations from the same plant, including marijuana but also hashish (derived from the resin of flowering somites) and cannabis oil. Cannabis has been used as a recreational drug for centuries and it is the most common illicit drug consumed in the world.(2,3)

The medical use of marijuana also goes back centuries. Marijuana was used for therapeutic purposes in China several millennia ago, with its first recorded use in a pharmacopeia appearing in 1500 BC. (4) Marijuana was customarily used to treat insomnia and as an antiemetic before the onset of specific therapies in the 1930s. Subsequently, marijuana has been labelled a drug of abuse in most countries worldwide. In Canada, marijuana was added to the restricted list under the Opium and Narcotic Drug Act by an amendment passed in 1923. Over the past two decades, there has been growing interest in the medical use of cannabis and its preparations in adults, along with increasing discussion around its potential for therapeutic use in children over the past five years.

The psychoactive properties of cannabis are primarily produced by delta-9-tetrahydrocannabinol (delta-9-THC), a cannabinoid

Le cannabis à des fins médicales est-il une option pour les enfants?

Le cannabis est une substance psychoactive utilisée depuis très longtemps dans un cadre récréatif et thérapeutique. Les considérations actuelles à l'égard de l'utilisation du cannabis à des fins médicales en pédiatrie découlent de récents rapports de cas sur son effet bénéfique lors d'une épilepsie réfractaire. Dans l'ensemble, les données sont insuffisantes pour en corroborer l'efficacité ou l'innocuité pour quelque indication que ce soit au sein de cette population, mais les données s'accumulent sur son potentiel néfaste, particulièrement pour traiter certaines affections. Il faut en évaluer soigneusement l'efficacité et l'innocuité comme agent thérapeutique contre certaines affections infantiles. L'inhalation sous forme de cigarette n'est pas un mode d'administration acceptable chez les enfants. L'utilisation de cannabis à des fins médicales dans des situations particulières ne doit pas en justifier l'utilisation à des fins récréatives chez les adolescents. Des recommandations sont formulées quant à son utilisation à des fins thérapeutiques dans des cas exceptionnels en pédiatrie, à condition d'assurer une évaluation étroite des sujets traités et de poursuivre des recherches bien conçues pour en déterminer l'innocuité et l'efficacité.

that is one of the two major neuroactive compounds found in marijuana.(5) The other major neuroactive compound, cannabidiol (CBD), lacks the psychoactive effects of delta-9-THC but does have behavioural and other central nervous system effects.(1) These compounds bind to G-protein coupled cannabinoid receptors on the membrane of cells in the central nervous system to produce their effects.(5)

NEW INFORMATION

Current status in Canada

Using marijuana for therapeutic purposes has included treatment for refractory epilepsy, described in case reports by Gowers and Reynolds from the late 19th century.(5) The development of more potent antiepileptic therapies and the trend toward marijuana prohibition reduced interest in marijuana as a therapy for refractory epilepsy. As time progressed, however, increasing knowledge of brain biology and the potent neuroactive properties of cannabinoids revived interest in its therapeutic potential. In 1996, California became the first American state to legalize the medicinal use of cannabis.(6) Several American states and the District of Columbia have subsequently legalized the use of cannabis for medical purposes, despite the United States Drug Enforcement Administration's designation of marijuana as a "schedule one"

Correspondence: Canadian Paediatric Society, 100-2305 St Laurent Boulevard, Ottawa, Ontario K1G 4J8. E-mail info@cps.ca, website www.cps.ca

drug, defined under statute as having “no currently accepted medical use and a high potential for abuse”. In Canada, medical use of marijuana was sanctioned by Health Canada in 2001, with revisions to the legislation in 2013 (www.gazette.gc.ca/rp-pr/p1/2014/2014-06-14/html/reg1-eng.php). Canadian patients can obtain access to cannabis for medical purposes by visiting a health care practitioner, who can provide documentation to present to a licensed producer, with licensure being regulated on a federal basis. The producer can then supply the patient with up to 30 days’ supply, to a maximum weight of 150 g of marijuana. A recent ruling by the Supreme Court of Canada and a subsequent response from Health Canada have effectively removed some restrictions on the form in which cannabis can be supplied to patients. These rulings should permit the therapeutic use of preparations such as specific cannabis oils.

Evidence supporting the therapeutic effect of cannabis in children with epilepsy is sparse. There are animal models demonstrating that delta-9-THC and CBD have anticonvulsant activity in animal models of epilepsy, with the caveat that some studies also demonstrated pro-convulsant activity in healthy animals.(5) In these models, tolerability was limited with respect to delta-9-THC due to psychotropic effects, while CBD was better tolerated. Overall, clinical evidence supporting the use of marijuana and other cannabis derivatives in children is very sparse. Individual case reports have been published; however, evidence tested in randomized or controlled trials is scant.(7,8) One recent Cochrane review identified four studies examining marijuana use for epilepsy.(9) A total of only 47 patients were studied, all of whom were adults. While these studies demonstrated short-term tolerance, no single study reliably demonstrated a reduction in seizure frequency. The authors concluded that the use of marijuana to treat epilepsy needed to be evaluated in properly designed and powered studies.

Much stronger data supports the limited efficacy of marijuana to treat other medical conditions. Studies investigating cannabis use to manage spasticity in adults with multiple sclerosis (MS) have shown that cannabinoids, administered orally, appear to reduce patient-reported spasticity scores, while smoked marijuana was of uncertain efficacy.(10) A similar result was obtained for central pain or painful spasms in adults with MS. There were fewer bladder complaints in adults with MS treated with nabiximols, one of three medications derived from cannabis and approved for use in Canada, although no effect was demonstrated using other oral cannabinoids. Cannabinoids also appeared to be ineffective for controlling tremors in adults with MS, chorea in adults with Huntington’s disease, levodopa-associated dyskinesia in adults with Parkinson’s disease or tics in adults with Tourette’s syndrome.(10)

Cannabis continues to be considered as a potential therapy in conditions for which there are, essentially, no data supporting its use. There have been no studies demonstrating the efficacy and safety of marijuana use to control children’s pain or nausea.(11)

Potent medications can be accompanied by significant, potentially adverse side effects. It is well recognized, for example, that many drugs commonly used for seizure therapy in children are also associated with negative effects on behaviour and learning. The most predictable side effects associated with marijuana use are red eyes, dry mouth, delayed motor skills and tachycardia;(12) however, reviews of the medical use of cannabis have also identified adverse events. A review of studies investigating marijuana use for selected neurological disorders demonstrated that 6.9% of 1619 patients treated with a cannabinoid for <6 months stopped use due to adverse events, compared with 2.2% of 1118 subjects in the control group.(10) While these effects were not well characterized,

they included nausea, weakness, mood changes and anxiety. Studies focused on cognitive impairment appeared to show twice the degree of cognitive impairment among patients treated with marijuana compared with controls.(10,13) Cannabinoid use in one randomized clinical trial involving patients with MS was associated with a higher suicide risk compared with placebo controls.(14) All of these studies involved adult patients. There is ongoing controversy regarding cannabis use being associated with a risk for serious mental health disorders such as psychosis. The data linking marijuana use with a higher risk for psychosis were highlighted in a recent study which demonstrated that up to one-quarter of cases of new-onset psychosis were associated with the recreational use of high-potency cannabis.(15,16)

There is a small body of literature suggesting that the magnitude of cognitive effects of cannabis may be age dependent. One small study focused on adolescents with attention deficit hyperactivity disorder who used marijuana regularly, and found an association with impaired executive function and, potentially, for impaired cognitive function when marijuana use was initiated before 16 years of age. When regular marijuana use was not started until after 16 years of age, there was no apparent aggravation of cognitive deficits associated with attention deficit hyperactivity disorder.(17) One neuroimaging study examining young adult recreational marijuana users showed differences in grey matter density, volume and shape compared with controls.(18) Chronic marijuana exposure is associated with adverse effects on the functional integrated relationship among spatially separated brain regions that may be exaggerated when exposure begins during adolescence.(12,19-21) While there are no data regarding the impact of cannabis use on the brains of younger children, it is probable that effects would be similar. Even these limited findings have implications for the medical use of cannabis in children.

In the context of recreational use, there are usually periods when the concentration of cannabinoids in the blood is low or minimal. In contrast, in a therapeutic context, such as using cannabis to manage intractable epilepsy, one goal would be to maintain a relatively constant concentration of cannabinoids in the bloodstream over time. Therefore, future research investigating cannabis use for medical purposes in children must include longitudinal developmental assessments, ideally with neuroimaging, and discussions about informed consent to participate in these studies need to include such considerations of effect. In conditions for which cannabis is used as a therapy of last resort, there should be a robust and complete discussion with the patient (when possible) and the family regarding the potential risks and benefits. The therapeutic course must be monitored closely for evidence of both efficacy and toxicity.

In common with many other potent psychotropic agents, marijuana use is associated with risk for dependence.(22) Risk levels range between 9% and 50% among recreational marijuana users and appear to be higher when marijuana use begins in adolescence and occurs on a daily basis.(21) Discontinuation of cannabis among chronic users is commonly associated with withdrawal symptoms including headaches, sleep disruption, irritability and anxiety.(23)

One issue germane to marijuana use for treating children is that it is usually smoked. There are several compelling reasons why smoking is an unacceptable drug delivery system for younger populations. Combustion produces tars and other by-products known to be associated with long-term harmful effects, most notably carcinogenesis. The delivery of drugs by smoking also makes it difficult to control or adjust dosage. This difficulty is especially relevant in that the THC content of marijuana available today is two to four times higher than from typical plants used decades ago.(21,24) There is

also considerable variability in THC content batch-to-batch.(21) Should cannabis be demonstrated to be an effective and safe therapy for selected health conditions in children, a more appropriate and stable dosing form other than smoking should be used. Recent rulings governing the availability of cannabis for medical purposes in Canada could open the way for other formulations.

As with other psychoactive agents, being able to demonstrate the efficacy and safety of cannabis use for medical purposes in thoughtfully designed, carefully monitored therapies for selected conditions in children is neither a rationale for, nor supportive of, the recreational use of marijuana by children or adolescents. One recent study from the United States that compared marijuana use in adolescents in states where cannabis for medical purposes was available with states where it was not, found there was no increase in recreational use where it was legal.(25) In contrast, a study in Colorado – where cannabis use for medical purposes is available – tracked attitudes toward and trends in marijuana use among adolescents, and demonstrated both lower risk-perception and a higher rate of marijuana use among 12- to 17-year-olds, compared with states where it was not available.(26) The same research group described a significant increase in motor vehicle fatalities where marijuana use was a factor following the legalization of marijuana for medical purposes in Colorado.(27)

If and when cannabis is proven to be therapeutically efficacious and safe, it must be regulated with the same care and precision as other psychoactive therapeutic agents.(28,29) The “medical marijuana” industry must also be subject to the same regulatory standards, legislative controls and degree of oversight as the pharmaceutical industry. Consideration of the particular safety issues germane to children must remain front and centre in the decision to treat exceptional paediatric cases.(30)

RECOMMENDATIONS

- While anecdotal evidence and biological plausibility suggest that cannabis and its derivatives may be an effective treatment for refractory epilepsy in children, its efficacy in this population should be carefully evaluated over the long-term, using appropriately supported and well-designed research into developmental effects, including neuroimaging (level of evidence: 4).(31)
- Medical evidence and biological plausibility suggest that therapeutic use of cannabis may have significant adverse effects in children. Risks should be carefully evaluated over the long-term, using appropriately supported and well-designed research into the safety issues specific to children,

REFERENCES

1. Radwan MM, Elsohly MA, Slade D, Ahmed SA, Khan IA, Ross SA. Biologically active cannabinoids from high-potency *Cannabis sativa*. *J Nat Prod* 2009;72(5):906-11.
2. United Nations Office on Drugs and Crime. World Drug Report 2014. United Nations publication, Sales No. E.14.XI.7.
3. Intiaz S, Shield KD, Roerecke M, et al. The burden of disease attributable to cannabis use in Canada in 2012. *Addiction* 2015 (E-pub ahead of print). Doi: 10.1111/add.13237.
4. Bell H. Medicine or menace? What we know about medical marijuana. *Minn Med* 2014;97(4):18-27.
5. Devinsky O, Cilio MR, Cross H, et al. Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia* 2014;55(6):791-802.
6. Milhofer J. Medical marijuana – coming soon to a medicine cabinet near you? Where the nation stands in terms of legalizing medical cannabis. *Minn Med* 2014;97(4):44-6.
7. Maa E, Figi P. The case for medical marijuana in epilepsy. *Epilepsia* 2014;55(6):783-6.

including development and neuroimaging studies (level of evidence: 3).

- Smoking as the customary mode of delivery for marijuana is unacceptable in children for several reasons. Studies investigating cannabis use for medical purposes in children should explore alternative delivery systems to provide safe and consistent drug concentrations (level of evidence: 3).
- While research is ongoing, the use of cannabis for medical purposes in children should be evaluated on a case-by-case basis, and always with a comprehensive discussion of potential benefits and risks. Treatment plans that include cannabis should be constructed with careful attention to dose-finding, evaluation of efficacy and safety monitoring, and should only be conducted by clinicians or health teams with condition-specific expertise and the ability to assess for, and evaluate, both efficacy and toxicity (level of evidence: 4).
- Using cannabis to treat neurological conditions in children should be evaluated in accordance with a careful research strategy. The decision to study cannabis use for a specific condition should always be based on the biological plausibility of efficacy and on evidence determined by well-designed clinical trials (level of evidence: 4).
- Clinicians who treat children with cannabis should have specific expertise and training in the use of potent psychoactive drugs in this population. Treatment should be predicated by robust discussions with the patient (if possible) and family concerning the goals and potential risks of this choice, with a strong monitoring strategy in place to test for efficacy and adverse effects.
- There is biological plausibility that cannabis may produce harm if used to treat certain conditions in children, especially when started at an early age (level of evidence: 4).
- The selective use of cannabis for medical purposes in children must not be confused with condoning its recreational use by adolescents. Strategies to discourage its recreational use among adolescents should be developed on models underway to discourage alcohol and tobacco use in this age group (level of evidence: 3).

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14. Zajicek JP, Fox P, Sanders H, et al; UK MS Research Group. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): Multicentre randomised placebo-controlled trial. *Lancet* 2003;362(9395):1517-26.
15. Di Forti M, Marconi A, Carra E, et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: A case-control study. *Lancet Psychiatry* 2015;2(3):233-8.
16. Crocker CE, Tibbio PG. Cannabis and the maturing brain: Role in psychosis development. *Clin Pharmacol Ther* 2015;97(6):545-7.
17. Tamm L, Epstein JN, Lisdahl KM, et al; MTA Neuroimaging Group. Impact of ADHD and cannabis use on executive functioning in young adults. *Drug Alcohol Depend* 2013;133(2):607-14.
18. Gilman JM, Kuster JK, Lee S, et al. Cannabis use is associated with nucleus accumbens and amygdala abnormalities in young adult recreational users. *J Neurosci* 2014;34(16):5529-38.
19. Zalesky A, Solowij N, Yücel M, et al. Effect of long-term cannabis use on axonal fiber connectivity. *Brain* 2012;135(Pt 7):2245-55.
20. Tortoriello G, Morris CV, Alpar A, et al. Miswiring the brain: Δ9-tetrahydrocannabinol disrupts cortical development by inducing an SCG10/stathmin-2 degradation pathway. *EMBO J* 2014;33(7):668-85.
21. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med* 2014;370(23):2219-27.
22. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet* 2009;374(9698):1383-91.
23. Budney AJ, Hughes JR. The cannabis withdrawal syndrome. *Curr Opin Psych* 2006;19(3):233-8.
24. Hadland SE, Knight JR, Harris SK. Medical marijuana: Review of the science and implications for developmental-behavioral pediatric practice. *J Dev Behav Pediatr* 2015;36(2):115-23.
25. Choo EK, Benz M, Zaller N, Warren O, Rising KL, McConnell KJ. The impact of state medical marijuana legislation on adolescent marijuana use. *J Adolesc Health* 2014;55(2):160-6.
26. Schuermeyer J, Salomonsen-Sautel S, Price RK, et al. Temporal trends in marijuana attitudes, availability and use in Colorado compared to non-medical marijuana states: 2003-11. *Drug Alcohol Depend* 2014;140:145-55.
27. Salomonsen-Sautel S, Min SJ, Sakai JT, Thurstone C, Hopfer C. Trends in fatal motor vehicle crashes before and after marijuana commercialization in Colorado. *Drug Alcohol Depend* 2014;140:137-44.
28. Richter KP, Levy S. Big marijuana – lessons from big tobacco. *N Engl J Med* 2014;371(5):399-401.
29. Crépault, J-F. Cannabis policy framework. Centre for Addiction and Mental Health, University of Toronto, 2014: www.camh.ca/en/hospital/about_camh/influencing_public_policy/Documents/CAMHCannabisPolicyFramework.pdf (Accessed December 3, 2015).
30. Expert panel on therapeutic products for infants, children and youth. Improving medicines for children in Canada. Council of Canadian Academies, 2014: www.scienceadvice.ca/uploads/eng/assessments%20and%20publications%20and%20news%20releases/therapeutics/therapeutics_fullreporten.pdf (Accessed December 3, 2015).
31. Sackett DL, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine: How to practice and teach EBM. New York: Churchill-Livingstone, 1997.

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Research

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Evaluation of herbal cannabis characteristics by medical users: a randomized trial

Mark A Ware*¹, Thierry Ducruet² and Ann R Robinson²

Address: ¹Departments of Anesthesia and Family Medicine, McGill University, Montreal, Quebec, Canada and ²Boreal Primum Inc., 913 Cherrier, Montreal, Quebec, Canada

Email: Mark A Ware* - mark.ware@muhc.mcgill.ca; Thierry Ducruet - t.ducruet@borealprimum.com; Ann R Robinson - a.robinson@borealprimum.com

* Corresponding author

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Abstract

Background: Cannabis, in herbal form, is widely used as self-medication by patients with diseases such as HIV/AIDS and multiple sclerosis suffering from symptoms including pain, muscle spasticity, stress and insomnia. Valid clinical studies of herbal cannabis require a product which is acceptable to patients in order to maximize adherence to study protocols.

Methods: We conducted a randomized controlled crossover trial of 4 different herbal cannabis preparations among 8 experienced and authorized cannabis users with chronic pain. Preparations were varied with respect to grind size, THC content and humidity. Subjects received each preparation on a separate day and prepared the drug in their usual way in a dedicated and licensed clinical facility. They were asked to evaluate the products based on appearance (smell, colour, humidity, grind size, ease of preparation and overall appearance) and smoking characteristics (burn rate, hotness, harshness and taste). Five-point Likert scores were assigned to each characteristic. Scores were compared between preparations using ANOVA.

Results: Seven subjects completed the study, and the product with highest THC content (12%), highest humidity (14%) and largest grind size (10 mm) was rated highest overall. Significant differences were noted between preparations on overall appearance and colour ($p = 0.003$).

Discussion: While the small size of the study precludes broad conclusions, the study shows that medical cannabis users can appreciate differences in herbal product. A more acceptable cannabis product may increase recruitment and retention in clinical studies of medical cannabis.

Background

It is now well-recognized that *Cannabis sativa* (marijuana, weed, pot) is being used by patients with chronic debilitating diseases such as HIV/AIDS [1], chronic non-cancer pain [2], epilepsy [3], multiple sclerosis [4] and amyotrophic lateral sclerosis [5] for the management of symptoms such as pain, nausea, poor sleep, anxiety and stress. Since 2002, cannabis for medical use has been produced

by Prairie Plant Systems Inc (PPS) under license to Health Canada [6]. Cannabis is cultivated for use in clinical trials, open-label safety studies [7], and for distribution to persons authorized under the Medical Marijuana Access Regulations (MMAR) to use marijuana for medical purposes [8]. A number of authorized persons using this product initially reported concerns about the product, include the dryness, grind size (defined as the size of the particles after

grinding raw herbal material), and tetrahydrocannabinol (THC) content of the cannabis material [9].

To improve the acceptability of the cannabis product provided to patients and to facilitate recruitment and retention of research subjects in clinical trials, Health Canada and PPS explored mechanisms to vary herbal cannabis products with varying levels of humidity, THC content, and grind size. This study was conducted to evaluate several herbal cannabis presentations in which dryness, grind size and THC content were varied. The aims of the study were to determine experienced users' preference for cannabis products, and to determine whether there was any consistent pattern towards a preferred product.

Methods

A randomized, double-blind study of cannabis products was undertaken over a six week period in June-July 2004. Subjects were all current holders of valid authorizations to possess cannabis under the Medical Marijuana Access Regulations, and were currently using cannabis for medical purposes. Subjects agreed not to drive to or from their scheduled appointments.

Four (4) different PPS preparations of *Cannabis sativa* were evaluated; an identical species was used for all preparations. THC content was varied by blending the flowering heads with leaves from lower down the plant. The product was milled using a dry conical mill (Quadro® Comill®, Waterloo, Ontario), with particle size varied using screens with circular holes of 5 or 10 mm diameter. Cannabis preparations were packaged at PPS in 30 gram bags and labeled as Presentation # 1 to Presentation # 4 prior to shipment to the site pharmacy. The site pharmacist weighed 1 g quantities of each preparation (LP 3200D scale, Sartorius, Canada). The drug was repackaged in plastic vials closed with a soft plastic/rubber top, which were then dispensed to the study nurse as needed on the days of use. The product was weighed and transferred from the original package to the dispensing container within 5 minutes, and the ambient temperature and humidity conditions in the pharmacy were recorded at the time of preparation (Digital Hygrometer DHM-010, Davidoff, Canada). The original package was resealed immediately after weighing the required amount of product.

The characteristics of the products were determined using a specially designed questionnaire. Items consisted of 5-point Likert scales and included physical characteristics (smell (0: very unpleasant; 4: very pleasant), humidity (0: unacceptably dry; 4: optimum humidity), appearance (0: looks very bad; 4: looks excellent), particle size (0: very poor, 4: excellent), colour (0: very poor, 4: excellent) and ease of preparation (0: very hard to use; 4: very easy to use) and smoking characteristics (hotness (0: very hot; 4:

very cool), harshness (0: very harsh; 4: very smooth), burn rate (0: burns too fast; 4: burns just right), and taste (0: worse possible taste; 4: best possible taste). An overall comparison to usual cannabis was made (0: much worse than usual cannabis; 4: much better than usual cannabis). A global assessment was performed on the final day at which subjects were asked to rank the products assessed in order of preference (0: worse; 4: best). Subjects were not asked about clinical parameters such as efficacy.

Eligible subjects were given a scheduled series of 4 appointments. Informed consent was signed at the first appointment. The subjects were randomly assigned to test one cannabis preparation per day over the four days. They were asked to assess physical characteristics of the drug prior to use. They were asked to prepare and use the cannabis in the manner to which they were accustomed. Within five minutes of use they were asked to comment on the harshness, hotness, burn rate and comparison with usual cannabis. Subjects remained in the cannabis laboratory for one hour after use before being allowed to return home by taxi. On the evening after each clinic visit the subjects were contacted at home by the research nurse to determine if they had additional comments or concerns regarding the product they evaluated that day.

It was estimated that recruiting 8 subjects would allow a basic and preliminary assessment of trends in perceptions of differences between product characteristics. This number of subjects was also feasible to recruit within the time period of the study. The data were double entered and validated in a dedicated and secure database. Data were entered without identifiers to protect confidentiality. Cannabis preparations were ranked according to user preferences on each item. All items were rated equally. A total rank score for each preparation was assigned. Ranks according to individual physical and smoking characteristics were examined. All statistical analyses were done using SAS (SAS Institute, North Carolina). Means, frequencies and a multiple analysis of variance (ANOVA) for cross-over design (proc mixed) were calculated to assess the comparison between products. Period effect was analyzed independently. Due to the small sample-size, no adjustments were made for multiple comparisons.

The study was conducted at a dedicated cannabis research laboratory at the Montreal General Hospital in the McGill University Health Centre (MUHC). The study was approved by the Research Ethics Committee of the McGill University Health Centre.

Results

Eight subjects were recruited for the study. No subject refused to participate, but one subject did not attend for the final visit and was excluded from the final analysis.

Therefore the final report is based on seven subjects who completed the study. Inclusion of the eighth subject in a limited analysis did not alter the overall direction of the results. The period effect could not be assessed in the main model because one subject missed one visit; however no overall differences were found on overall comparison of the four time periods.

There were 5 males and 2 females, and the mean age was 47 years (range 40–54 y). Diagnoses were varied and included peripheral neuropathic pain (4 subjects), multiple sclerosis (2 subjects), and HIV/AIDS (1 subject).

The overall results based on the Likert scores for each characteristic and the overall scores are shown in Table 1. Product 1 (10.6% THC, 14.4% humidity, 10 mm grind size) was the most well rated product, and significant differences were noted between products overall ($p = 0.03$), and for physical characteristics including general appearance ($p = 0.03$) and colour ($p = 0.03$).

Of the 28 different assessments (7 subjects using 4 products), 18 were performed using joints and 10 using pipes. Most assessments (93%) were done with subjects reporting using the same amount of cannabis as usual, and 16/18 stated no problems in preparing their joints. Product 4 received a poor rating in terms of problems rolling it by 2 subjects.

Physical characteristics

Product 2 was treated as having the best smell with 6 subjects rating it pleasant or very pleasant. Product 2 was also rated as the best humidity with 6 subjects rating it acceptable. In general appearance, product 1 was superior; 4 subjects rated product 3 as 'looks bad'. Products 1, 2 and 3 were rated similar in terms of ease of preparation, although all 7 subjects rated products 1 and 2 as easy or very easy to use. Products 1 and 2 were rated equally in terms of colour. Product 1 was rated best in terms of particle size with 5 subjects rating particle size as good or excellent.

Smoking characteristics

Product 3 was rated most 'cool' overall. Product 2 was rated highest in terms of harshness with 6 subjects rating it as moderate or smooth. Product 1 was rated as having the best burn rate (1 subject stated it 'burned just right'), while each of products 2, 3 and 4 were rated by one subject each as burning too fast. Product 2 was rated as having the best overall taste.

Global assessments

Fourteen out of 28 (50%) subjects rated products 1, 3 and 4 as 'worse than their usual cannabis', 11 assessments were the 'same as usual cannabis' (4 of which were for product 2). Only 3 assessments were 'better than usual cannabis' (products 1, 2 and 4). Globally, product 1

Table 1: Evaluation of four cannabis preparations by physical and smoking characteristics*

Characteristic	Product				p-value	Contrasts
	1	2	3	4		
<i>Cannabis preparation</i>						
THC (g%)	10.6	10.6	6.6	9.6		
Humidity (%)	14.4	12	11	11		
Drying time (days)	2	4	4	4		
Grind size (mm)	10	5	5	10		
<i>Physical</i>						
Smell	2.71	3.00	2.57	2.43	0.21	
Humidity	1.71	1.86	1.71	1.14	0.28	
General appearance	2.71	2.29	1.43	1.86	0.03	1>3,4
Ease of preparation	3.29	3.14	3.29	2.86	0.55	
Colour	2.71	2.71	2.00	2.43	0.03	1,2>3
Particle size	2.86	2.43	1.57	1.86	0.06	
<i>Smoking</i>						
Hotness	1.86	1.86	2.14	1.86	0.81	
Harshness	2.14	2.14	1.43	1.71	0.53	
Burn rate	2.57	2.29	1.86	2.00	0.55	
Taste	2.00	2.14	1.29	2.00	0.41	
TOTAL SCORE	24.57	23.86	19.29	20.14	0.03	1,2>3,4

*Characteristic scores based on 5-point Likert scales (0–4). Higher scores reflect better ratings for each characteristic. See text for details.

received the highest score in terms of all the product characteristics measured (Table 2). In this overall analysis, product 1 was superior to products 3 and 4, and product 2 was superior to product 3.

Of the products tested, over half (4/7) of those using products 1 and 2 would use it on a regular basis, and over half would not use products 3 (5/7) and 4 (5/6) on a regular basis. In terms of overall satisfaction, 3 subjects rated product 1 as good or excellent and 2 subjects rated the other products as good or excellent. Five subjects rated product 3 as poor, and one rated product 2 as very poor.

Ambient humidity and temperature

The drug samples were prepared the day before the visit for the first 5 patients, resulting in the drug being in the new container for 16 to 20 hours. For the last 3 patients, the drug spent from 6 to 17 days in the new container. Temperature and humidity measurements were taken in the pharmacy on 14 days over the 28 day period. Over this period, the mean room temperature was 22.4°C (SD 0.23), and the mean ambient humidity was 46% (SD 4.4).

Discussion

To our knowledge, this is the first ever evaluation of medical cannabis products for physical and smoking characteristics by authorized patients. We have shown that subjects may appreciate differences between cannabis preparations on the basis of physical characteristics of the herbal material, specifically general appearance and colour. We did not show differences in individual smoking characteristics, but overall impressions confirmed that subjects favoured higher THC content, higher humidity and larger grind size.

The results of this study must be interpreted with considerable caution as there are many limitations to the data obtained. The small sample size reduces the power of the study to reach definitive conclusions about patient preference. The detected differences between products could have arisen by chance, or may have been influenced by other factors such as the use of different modes of administration (pipes and joints). Further study should limit the modes of administration to reduce confounding by these factors.

The effect of room air on the humidity levels of the product is a factor which may affect the validity of the final results. The average ambient humidity at the time of product preparation was well above that of the original product specifications (46% versus 10–15%), and could have raised the humidity of the product during the storage period prior to use. This would have the effect of reducing or eliminating the potential differences between products on humidity-based assessments. This may partially

explain why differences in physical characteristics such as colour, particle size and general appearance were detected (Table 2), while the hotness, harshness and burn rate appeared to be rated similarly between products.

Subjects' evaluations of smoking characteristics of the samples immediately after use may have been influenced by the psychoactive effects of cannabis. This study recruited experienced medicinal cannabis users who would likely evaluate any cannabis product under similar conditions ('try it and see') so we feel our approach is pragmatic and relevant.

The subjects and investigators were initially blind to the characteristics of the allocated products, but the ability of the subjects to differentiate the products suggests that the blinded condition was compromised. The investigators (study nurse or physician) did not evaluate their own ability to differentiate the products

In spite of these potential limitations, this randomized double-blind study has found that two of these products (products 1 and 2) could be appreciated differently from the other two, in terms of their physical and smoking characteristics. Product 3, which was a 10% THC blend (expiry date June 2004) which had been originally shipped by Health Canada to authorized patients was rated poorly by the subjects in this study, suggesting that the product could be improved by changing physical characteristics such as blending, particle size and humidity. These changes may result in improved patient satisfaction with the product, which may in turn increase the number of patients willing to use the Health Canada product and improve compliance in long term studies using the product. The study results support a decision by Health Canada, made prior to the study in May 2004, to distribute a product made only of flowering head material, taking into account preliminary reports from authorized users, with larger grind size, higher humidity and higher THC content. A review of Health Canada statistics [10] suggests that use of the Health Canada product increased since the new product was shipped in the summer of 2004 (Figure 1). An initial delay in uptake may have been due to media reports from disgruntled users about the poor quality of the product [11].

This study should ideally be repeated with larger numbers to validate differences between products. The reliability of the subjects' reports may also be validated by repeating the test with the same subjects and products to see if there is reliability between their assessments over time. Future studies of the effect of humidity could be done with subjects removing cannabis directly from an unopened original package prior to use rather than going through pharmacy dispensing. Methods of rehumidification of

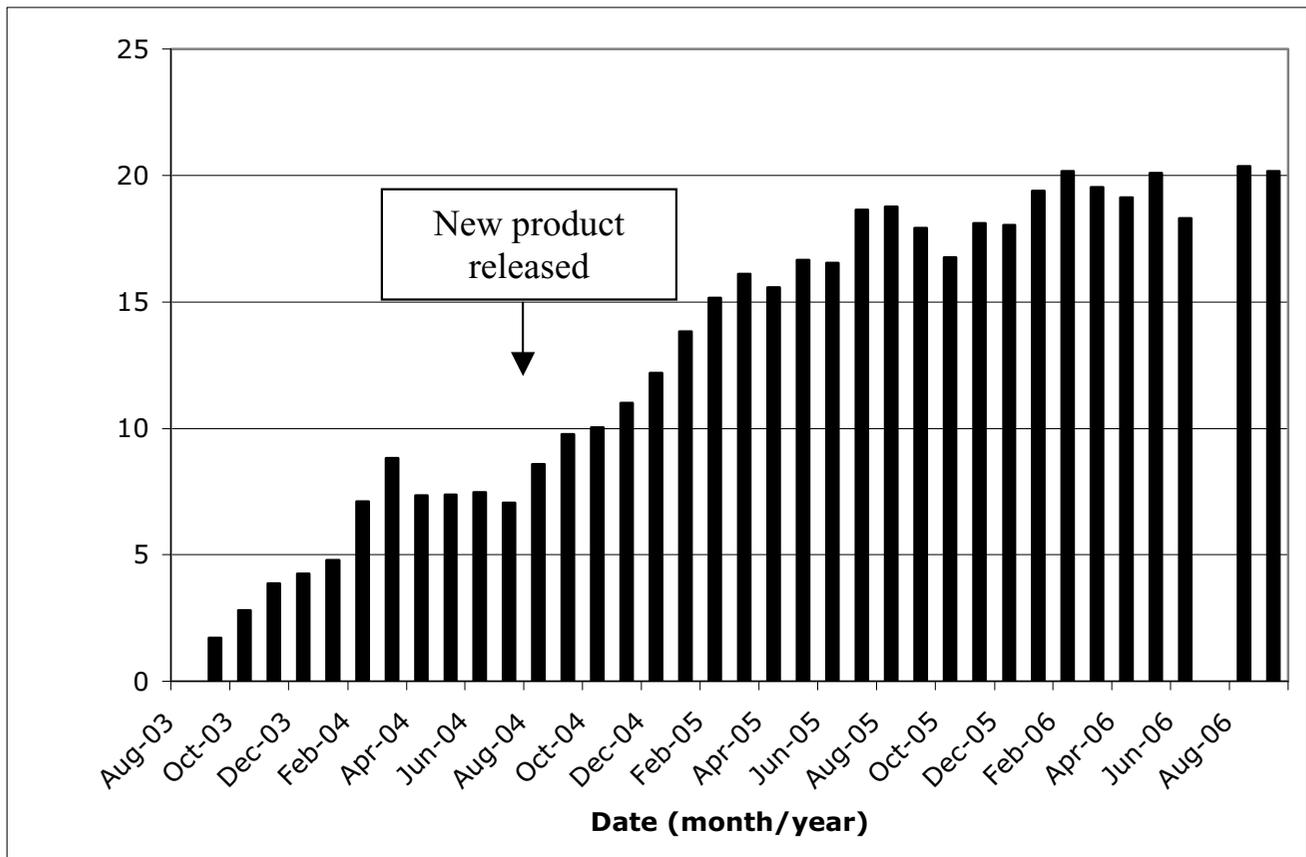


Figure 1
Percentage of authorized users obtaining herbal cannabis from Health Canada (data to Sept 2006)¹⁰.

herbal material should be explored. Finally, this study design may also be used to detect differences between cannabis products with different cannabinoid profiles or phenotypic characteristics.

Conclusion

We have shown that medical cannabis users may discriminate between cannabis preparations based on physical characteristics such as humidity, grind size, and smoking characteristics. The supply of a standardized herbal cannabis product within a legal medical access program needs to be guided by user's feedback to ensure compliance. Further work is required on other characteristics such as the profile of cannabinoids and other constituents.

Authors' contributions

The study was designed and supervised by Dr. Mark Ware, who prepared the final report and who is responsible for the work. Study management, including coordination, data collection, data entry and statistical analysis, was provided under subcontract to Boreal Primum Inc.

Competing interests

Dr Ware has received speakers fees, honoraria and grant support from companies developing cannabinoid products (AstraZeneca, Bayer, Cannasat, GW Pharma, Solvay and Valeant).

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References

1. Ware MA, Rueda S, Singer J, Kilby D: **Cannabis use by persons living with HIV/AIDS: patterns and prevalence of use.** *J Can Therapeut* 2003, **3(2)**:3-15.
2. Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ: **Cannabis use for chronic non-cancer pain: results of a prospective survey.** *Pain* 2003, **102(1-2)**:211-6.
3. Gross DW, Hamm J, Ashworth NL, Quigley D: **Marijuana use and epilepsy: prevalence in patients of a tertiary care epilepsy center.** *Neurology* 2004, **62(11)**:2095-7.

4. Clark AJ, Ware MA, Yazer E, Murray TJ, Lynch ME: **Patterns of cannabis use among patients with multiple sclerosis.** *Neurology* 2004, **62(11)**:2098-100.
5. Amtmann D, Weydt P, Johnson KL, Jensen MP, Carter GT: **Survey of cannabis use in patients with amyotrophic lateral sclerosis.** *Am J Hosp Palliat Care* 2004, **21(2)**:95-104.
6. **Health Canada. Prairie Plant Systems Inc, 2002** [http://www.hc-sc.gc.ca/dhp-mps/marihuana/supply-approvis/index_e.html]. Accessed 16th Nov 2006
7. **Health Canada. Marijuana Open Label Safety Initiative, 2003** [<http://www.cihr-irsc.gc.ca/e/4628.html>]. Accessed 16th Nov 2006
8. **Health Canada. Marijuana Medical Access Regulations, 2002** [<http://laws.justice.gc.ca/en/C-38.8/SOR-2001-227/text.html>]. Accessed 15 July 2004
9. **CBC. Government pot's the pits, 2003** [http://www.cbc.ca/stories/2003/09/16/canada/bad_dope030916]. Accessed July 15th 2004
10. **Health Canada: Stakeholder statistics** [http://www.hc-sc.gc.ca/dhp-mps/marihuana/stat/index_e.html]. Accessed Nov 10th 2006
11. **Federal pot pooh-pooed.** Dean Beeby (Canadian Press) in Globe and Mail. 12 July 2004

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Effects of cannabis on cognitive function in patients with multiple sclerosis

Kimia Honarmand, BSc
Mary C. Tierney, PhD,
CPsych
Paul O'Connor, MD
Anthony Feinstein, PhD,
MD

Address correspondence and
reprint requests to Dr. Anthony
Feinstein, University of Toronto,
27 King's College Circle,
Toronto, Ontario, Canada
M5S 1A1
ant.feinstein@utoronto.ca

ABSTRACT

Background: While neuropsychological deficits have been reported in healthy individuals who use street cannabis, data in patients with multiple sclerosis (MS) are lacking. Given that MS is associated with cognitive deterioration, the aim of this study was to determine the neuropsychological effects of cannabis use in this population.

Methods: Two groups, each of 25 patients with MS (cannabis users and nonusers), were administered the Minimal Assessment of Cognitive Function in MS battery of neuropsychological tests, the Hospital Anxiety and Depression Scale (HADS), and the Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I). Group-matching and regression analysis were used to control for the effects of age, sex, education, premorbid intelligence, disability, and disease course and duration on cognitive function.

Results: Cannabis users performed significantly more poorly than nonusers on measures of information processing speed, working memory, executive functions, and visuospatial perception. They were also twice as likely as nonusers to be classified as globally cognitively impaired. There were no between-group differences on the HADS measures of depression and anxiety or lifetime SCID-I psychiatric diagnoses.

Conclusion: This cross-sectional study provides empirical evidence that prolonged use of inhaled or ingested street cannabis in patients with MS is associated with poorer performance on cognitive domains commonly affected in this population. Whatever subjective benefits patients may derive from using street cannabis (e.g., pain and spasticity relief) should be weighed against the associated cognitive side effects. *Neurology*® 2011;76:1153-1160

GLOSSARY

ANART = American National Adult Reading Test; **BVMT-R** = Brief Visuospatial Memory Test-Revised; **COWAT** = Controlled Oral Word Association Test; **CVLT-II** = California Verbal Learning Test-Revised; **D-KEFS** = Delis-Kaplan Executive Function System; **EDSS** = Expanded Disability Status Scale; **HADS** = Hospital Anxiety and Depression Scale; **JLO** = Judgment of Line Orientation; **MACFIMS** = Minimal Assessment of Cognitive Function in MS; **MFIS** = Modified Fatigue Impact Scale; **MS** = multiple sclerosis; **PASAT** = Paced Auditory Serial Addition Test; **SDMT** = Symbol Digit Modalities Test; **SCID-I** = Structured Clinical Interview for the DSM-IV Axis I Disorders.

Cannabis research in patients with multiple sclerosis (MS) has largely focused on synthetic derivatives of the drug. The clinical trials literature is small and suggests treatment may have some mildly beneficial effects particularly in alleviating pain¹ and bladder dysfunction,² but equivocal benefits for spasticity.³ The only clinical trial specifically focused on cognition as the primary outcome measure failed to find any cognitive deficits associated with use of a cannabis-based extract.⁴

Even less attention has focused on inhaled “street” cannabis. Data show that 36%–43% of patients with MS have at some time smoked cannabis.^{5,6} The figure for current use, 14%–18%, is more modest, but indicates that a substantial minority of patients with MS find cannabis helpful for relief from pain, spasticity, insomnia, bladder problems, tremors, and emotional distress.^{5,6}

From the University of Toronto (K.H., M.C.T., P.O., A.F.), Toronto; Sunnybrook Health Sciences Centre (K.H., M.C.T., A.F.), Toronto; and St. Michael's Hospital (P.O.), Toronto, Canada.

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The benefits reported above are, however, subjective, and whether they are offset by potentially adverse cognitive effects has yet to be determined. A single pilot study suggested that MS cannabis smokers had further compromise with respect to information processing speed compared to nonusers.⁷ Given that approximately 40%–60% of patients with MS are cognitively impaired to begin with,^{8,9} any drug that may add to this burden gives cause for concern. The purpose of our study, therefore, was to examine the neuropsychological effects of inhaled or ingested cannabis on cognition in patients with MS.

METHODS **Sample selection.** Patients between the ages of 18 and 65 with confirmed MS¹⁰ were recruited from tertiary care MS clinics affiliated with the University of Toronto. Exclusion criteria included history of traumatic brain injury, psychotic illness, concurrent neurologic diseases, and poor visual acuity (less than 20/70 corrected, both eyes). Those who had undergone neuropsychological testing within the last year were also excluded in order to avoid possible practice effects.

Cannabis sample. Subjects who used cannabis recently and whose urine tested positive for cannabinoids only (i.e., no other illicit drugs were permissible) on the day of assessment were included. Subjects who reported cannabis use less than 12 hours prior to testing were excluded.

In addition, a history of cannabis use including age at onset, duration, and frequency of cannabis use was recorded for all subjects. The reasons for smoking cannabis were divided into 3 categories: medical, recreational, or a combination.

Control sample. MS cannabis users were group-matched (on age, sex, Expanded Disability Status Scale [EDSS], disease course and duration, level of education, and premorbid IQ based on the American National Adult Reading Test [ANART]) to a control group of 25 noncannabis-using patients with MS derived from a larger control sample of 38 cannabis-naïve subjects with MS. The control group was made up of subjects with MS who reported no recent history of cannabis use and had urine that tested negative for cannabinoids and other illicit drugs. A remote history of occasional teenage use was not an exclusionary factor.

Urinalysis. A broad-spectrum analysis was conducted to determine the presence of the following substances: cannabis, cocaine, opiates, amphetamines, and phencyclidine. The cannabinoid assay detects 11-nor- Δ -9-tetrahydrocannabinol-9-carboxylic acid-B glucuronide (THC-COOH glucuronide) and 11-nor- Δ -9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH) in urine. These levels are combined to provide a composite score.

Demographic and neurologic data. Demographic and disease-related variables, namely age, sex, education, marital or partner status, employment status, disease course, disease duration, and current medications were collected from each patient and their medical charts. Neurologic disability according to the EDSS¹¹ was recorded from patient files. Alcohol consumption referred to the total number of drinks (a glass of wine, shot of spirits, or standard bottle [330 mL] of beer) consumed weekly. Visual acuity was assessed using the Rosenbaum Pocket Screener.

Psychiatric assessment. The presence of lifetime psychiatric disorders was established using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Mood and Anxiety Disorder sections.¹² In addition, all subjects completed the Hospital Anxiety and Depression Scale (HADS), validated for use with patients with MS.¹³ Fatigue was measured using the Modified Fatigue Impact Scale (MFIS).¹⁴

Neuropsychological assessment. Premorbid intellectual functioning was assessed with the ANART.¹⁵ Thereafter, patients were administered the Minimal Assessment of Cognitive Function in MS (MACFIMS), a comprehensive battery of 7 tests measuring 11 cognitive indices considered optimum for teasing out deficits in this population.¹⁶ The MACFIMS is regarded as the gold standard for cognitive assessment in MS and was put together by consensus following a meeting of leading neuropsychologists involved in MS research.¹⁷ The battery includes the following tests: verbal learning and memory: The California Verbal Learning Test–Revised (CVLT-II)¹⁸; visuospatial memory and learning: Brief Visuospatial Memory Test–Revised (BVRT)¹⁹; visual perception/spatial processing: the Judgment of Line Orientation (JLO)²⁰; verbal fluency/word retrieval: the Controlled Oral Word Association Test (COWAT)²¹; executive functions: the Delis-Kaplan Executive Function System (D-KEFS) Sorting Test²²; information processing speed and working memory: the Paced Auditory Serial Addition Test (PASAT)^{8,23} with 3.0- and 2.0-second interstimulus intervals; information processing speed: the Symbol Digit Modalities Test (SDMT).²⁴

As specified in the MACFIMS validation data,¹⁷ global cognitive impairment represents failure on 2 or more of 11 cognitive indices. Impairment on a single test is defined as a z score of 1.5 or more below norms derived from age-, sex-, and education-matched healthy control subjects. These normative data are provided in the test manuals.

Statistical analyses. Primary analysis included between-group comparisons with t tests and χ^2 analyses. The Mann-Whitney U test was used for non-normally distributed variables.

Further cognitive comparisons between cannabis users and nonusers were performed with a series of linear regression analyses, with each of the 11 cognitive indices as the dependent variable and cannabis use as the independent variable. Age, sex, education, EDSS, alcohol consumption, depression, anxiety, and fatigue were entered sequentially into the analysis as covariates. These variables were selected due to their potential effects on cognition. Only covariates that changed the group coefficient by 10% or more were retained in the final model for each cognitive measure.

Similarly, binary logistic regression analysis was conducted to investigate the effect of cannabis use on global cognitive impairment after controlling for the potential confounds mentioned above. As before, only covariates that changed the group coefficient by 10% or more were retained in the final model.

Pearson correlations were conducted to determine the association between age at onset of cannabis use, duration of cannabis use, and urine cannabinoid levels on the one hand and global cognitive impairment on the other. χ^2 Analysis was used to determine the association between duration of abstinence (12–24 hours vs greater than 24 hours) and global cognitive impairment.

Standard protocol approvals, registrations, and patient consents. Ethics approval for the study was obtained from Research Ethics Boards at Sunnybrook Health Sciences Centre and St. Michael's Hospital, both affiliated with the University of To-

Table 1 Demographic and neurologic variables for MS cannabis users and nonusers

Sample characteristics	Cannabis users	Nonusers	t or χ^2	p
Age, y, mean (SD)	43.6 (11.7)	43.6 (9.8)	t = 0.000	1.000
F/M	11/14	12/13	$\chi^2 = 0.081$	0.777
Education, y, mean (SD)	13.5 (2.8)	14.6 (2.8)	t = -1.482	0.145
ANART, mean (SD)	108.6 (9.7)	112.5 (7.1)	t = -1.581	0.120
Employment status, n (%) currently employed	7 (28.0)	14 (56.0)	$\chi^2 = 4.023$	0.045
Marital status, n (%) married/common-law	16 (64.0)	17 (68.0)	$\chi^2 = 0.089$	0.765
Disease duration, y, mean (SD)	11.4 (7.6)	12.7 (11.0)	t = -0.479	0.634
Disease course, n				
Relapsing-remitting	17	19	$\chi^2 = 0.422$	0.810
Primary/secondary progressive	3/5	2/4		
EDSS, median (range)	3.0 (0-8.5)	2.0 (0-8.0)	t = 1.186	0.241
Disease-modifying drugs, n (%)	11 (44.0)	9 (36.0)	$\chi^2 = 0.333$	0.564
Alcohol, n/wk, median (range)	2.5 (0-12)	1.0 (0-8)	t = 1.870	0.068

Abbreviations: ANART = American National Adult Reading Test; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.

ronto. All participants provided written informed consent prior to participating in the study. Patients were clearly informed of the aim of the study, namely to examine the effect of cannabis use on neuropsychiatric functioning in MS.

RESULTS Demographics and neurologic variables.

Entire sample. The sample consisted of 25 cannabis users (11 women) and 25 nonusers (12 women). The mean age of the entire sample was 43.60 (SD 10.7). Thirty-three patients (66.0%) were married or cohabitating and 21 (42.0%) were employed. Patients had received an average of 14.0 years (SD 2.8) of education. Average disease duration was 12.1 years (SD 9.4). The breakdown of disease course was as follows: relapsing-remitting 72.0%; secondary progressive 18.0%; primary progressive 10.0%. The median EDSS score was 3.0 (mean 3.32, SD 2.39, range 0-8.5). Twenty patients (40.0%) were taking

Table 2 Comparison of MS cannabis users and nonusers on psychiatric measures

Variable	Cannabis users, mean (SD)	Nonusers, mean (SD)	t or χ^2	p
SCID-I major depression, lifetime, n (%)	15 (60.0)	13 (52.0)	$\chi^2 = 0.325$	0.569
SCID-I anxiety disorder, lifetime, n (%)	10 (40.0)	8 (32.0)	$\chi^2 = 0.347$	0.556
Antidepressants, n (%) taking	10 (40.0)	12 (48.0)	$\chi^2 = 0.325$	0.569
HADS depression subscore	7.0 (4.4)	6.7 (4.9)	t = 0.182	0.856
HADS anxiety subscore	8.8 (4.7)	7.00 (5.7)	t = 1.225	0.227
Modified Fatigue Impact Scale	46.3 (16.2)	40.4 (24.2)	t = 1.022	0.322

Abbreviations: HADS = Hospital Anxiety and Depression Scale; MS = multiple sclerosis; SCID-I = Structured Clinical Interview for the DSM-IV axis I disorders.

disease-modifying drugs. Patients consumed a median of 2.0 alcoholic beverages per week (mean 3.0, SD 3.3, range 0-12). Four subjects had taken steroids within the last 3 months.

Comparison between cannabis users and nonusers. Comparisons between cannabis users and nonusers on demographic and disease-related variables are presented in table 1. There were no statistically significant group differences for age, sex, years of education, marital status, EDSS, disease course, duration of MS, and use of disease-modifying drugs. Cannabis users were significantly more likely to be unemployed. Cannabis users also reported slightly higher alcohol consumption compared to nonusers, although this difference did not reach statistical significance.

Cannabis use. The average age at onset of cannabis use was 17.0 years (median 15.0, SD 6.6, range 13-47) and the average duration of cannabis use was 26.6 years (median 31.0, SD 12.1, range 1-41). Eighteen subjects (72.0%) used cannabis on a daily basis, 6 (24.0%) reported weekly use, and one reported biweekly use. Most cannabis users (n = 24) reported inhalation (smoking or vaporization) whereas one reported consumption of food products containing cannabis. Eight subjects (32.0%) reported using cannabis for medicinal reasons, 3 (12.0%) for recreational reasons, and 14 (56.0%) for a combination.

Mean level of urine cannabinoid metabolites was 174.4 $\mu\text{g/L}$ (SD 40.8, range 61- ≥ 200) and the broad-spectrum drug screen indicated that no subject had used any illicit drugs other than cannabis. The period of abstinence from cannabis use ranged from 12 hours to 14 days prior to testing with most patients (n = 18) reporting their last use on the evening prior to testing. The remaining 7 subjects had not used cannabis for more than 24 hours.

Urine drug screening indicated that none of the noncannabis users tested positive for cannabinoids or any other nonmedicinal substances.

Psychiatric assessment. The lifetime prevalence of major depression for the entire sample was 56.0%. Lifetime prevalences for anxiety disorders were as follows: generalized anxiety disorder 26.0%; panic disorder 20.0%; phobia 4.0%; obsessive compulsive disorder 2.0%; and post-traumatic stress disorder 4.0%. Lifetime prevalence for any of the anxiety disorders was 36.0%.

Psychiatric comparison between cannabis users and nonusers is presented in table 2. There were no significant differences between groups in the lifetime prevalences of psychiatric disorders and use of antidepressant medication. Similarly, scores on HADS

Table 3 Cognitive test comparisons between MS cannabis users and nonusers

Cognitive domain	Cognitive test	Cannabis users, mean (SD)/n (%) impaired	Nonusers, mean (SD)/n (%) impaired	t or χ^2	p
Learning and memory	CVLT-II immediate recall	49.5 (10.9)	52.5 (11.2)	t = -0.969	0.337
	CVLT-II long delay recall	10.6 (3.6)	11.2 (2.7)	t = -0.681	0.499
	BVMT-R total recall	22.1 (8.3)	22.8 (7.6)	t = -0.284	0.777
	BVMT-R delayed recall	8.2 (3.1)	8.7 (3.1)	t = 0.545	0.588
Verbal fluency	COWAT total score	31.0 (11.9)	33.7 (10.8)	t = -0.845	0.403
Visuospatial perception	JLO score ^a	23.9 (4.7)	26.7 (3.5)	t = -2.417	0.020
Executive functioning	D-KEFS sorting score	8.4 (2.4)	10.3 (2.7)	t = -2.704	0.009
	D-KEFS description score	31.4 (9.5)	37.4 (10.4)	t = -2.127	0.039
Information processing speed	PASAT 3.0	36.0 (12.0)	44.0 (11.4)	t = -2.402	0.020
	PASAT 2.0	26.1 (7.6)	35.0 (11.7)	t = -3.188	0.003
	SDMT Total	42.4 (11.4)	50.4 (12.9)	t = -2.329	0.024
Global cognitive impairment	≤1.5 SD on 2 or more of 11 cognitive tests, n (%)	16 (64.0)	8 (32.0)	$\chi^2 = 5.128$	0.024

Abbreviations: CVLT = California Verbal Learning Test; BVMT-R = Brief Visuospatial Memory Test-Revised; COWAT = Controlled Oral Word Association Test; JLO = Judgment of Line Orientation; D-KEFS = Delis-Kaplan Executive Functions Test; MS = multiple sclerosis; PASAT = Paced Auditory Serial Addition Test; SDMT = Symbol Digit Modalities Test.

^a JLO score corrected for sex and age.

Depression and Anxiety subscales and the MFIS showed no significant differences between cannabis users and nonusers (table 2).

Neuropsychological assessment. Neuropsychological comparisons between cannabis users and nonusers are presented in table 3. Cannabis users scored significantly lower on the PASAT-3, PASAT-2, JLO, SDMT, and D-KEFS Sorting Test and Description scores. There were no between-group differences on CVLT-immediate recall, CVLT-delayed recall, BVMT-immediate recall, BVMT-delayed recall, and COWAT.

Of all 50 patients, 24 (48.0%) were classified as cognitively impaired. Cannabis users were significantly more likely to be classified as globally impaired compared to nonusers ($\chi^2 = 5.13$, $p = 0.024$; table 3).

Although the cannabis users and nonusers were group-matched on demographic and disease-related variables, we further analyzed our data with the aim of exploring the effect of cannabis use on each cognitive measure independent of age, sex, education, alcohol consumption, EDSS, depression, anxiety, and fatigue. The final regression models reveal that cannabis use remained a significant independent predictor of performance on the PASAT-2, JLO, SDMT, D-KEFS Sorting Score, and global cognitive impairment, but not on CVLT-immediate recall, CVLT-delayed recall, BVMT-immediate recall, BVMT-delayed recall, COWAT, PASAT-3, and D-KEFS Description Score (table 4). Exclusion of the one

subject who indicated only ingesting cannabis in food products did not significantly alter the findings.

Global cognitive impairment was not significantly correlated with urine cannabinoid levels ($r = -0.321$, $p = 0.118$), age at cannabis use onset ($r = -0.321$, $p = 0.118$), or duration of cannabis use ($r = 0.158$, $p = 0.451$). The period of abstinence from cannabis use was not associated with global cognitive impairment ($\chi^2 = 0.198$, $p = 0.673$).

DISCUSSION The specific aim of this prospective study was to examine the effects of smoked or ingested cannabis on cognitive function in patients with MS. We found that cannabis users had greater deficits on information processing speed, working memory, executive function, and visuospatial perception compared to a sample of nonusers group-matched on age, sex, education, premorbid intelligence, EDSS, and disease course. Cannabis users were also twice as likely as nonusers to meet criteria for global cognitive impairment. Most of these between-group differences were retained after controlling for potential confounds.

Cognitive dysfunction affects approximately 40%–60% of patients with MS^{8,9} with detrimental effects on personal, social, and occupational functioning.⁸ Cognitive functioning is also a major determinant of quality of life.²⁵ Given these adverse psychosocial effects, identifying risk factors associated with further cognitive impairment is important. Although not the focus of the present investigation,

Table 4 Linear regression analyses for significant cognitive tests and cannabis use^a

Cognitive domain	Cognitive test indices	Covariates ^b	B (95% CI)	p
Learning and memory	CVLT-II immediate recall	Sex, education, EDSS, alcohol consumption, HADS anxiety	1.451 (–5.093 to 7.995)	0.657
Verbal fluency	CVLT-II long delay recall	Sex, education, EDSS, alcohol consumption, HADS anxiety, MFIS	0.399 (–1.286 to 2.084)	0.635
Visuospatial perception	BVMT-R total recall	Sex, education, EDSS, alcohol consumption, HADS anxiety, MFIS	–0.315 (–5.156 to 4.526)	0.896
Executive functioning	BVMT-R delay recall	Education, EDSS, alcohol consumption, HADS anxiety, MFIS	0.215 (–1.806 to 2.235)	0.831
Information processing speed	COWAT total score	Sex, Education, EDSS, HADS anxiety, MFIS	1.832 (–5.115 to 8.779)	0.533
Global cognitive impairment	JLO score	HADS anxiety, MFIS	2.904 (0.545 to 5.263)	0.017
	D-KEFS sorting score	Education, alcohol consumption	1.676 (0.274 to 3.077)	0.020
	D-KEFS description Score	Education, EDSS, alcohol consumption	4.943 (–0.663 to 10.548)	0.083
	PASAT -3.0	Sex, education, alcohol consumption, HADS anxiety	4.355 (–2.600 to 11.310)	0.214
	PASAT 2.0	Education	8.007 (2.347 to 3.667)	0.007
	SDMT total	EDSS, alcohol consumption	7.116 (0.337 to 13.895)	0.040
	≤1.5 SD on 2 or more of 11 cognitive tests, n (%)	Education	–1.468 (1.265 to 14.887)	0.020

Abbreviations: BVMT-R = Brief Visuospatial Memory Test–Revised; CI = confidence interval; COWAT = Controlled Oral Word Association Test; CVLT = California Verbal Learning Test; EDSS = Expanded Disability Status Scale; HADS = Hospital Anxiety and Depression Scale; JLO = Judgment of Line Orientation; D-KEFS = Delis-Kaplan Executive Functions Test; MFIS = Modified Fatigue Impact Scale; PASAT = Paced Auditory Serial Addition Test; SDMT = Symbol Digit Modality Test.
^a All models contained group as a predictor. Model parameters are presented for cannabis group after controlling for confounds.

^b Only variables that changed the coefficient for cannabis group by 10% or more were retained in the final model as covariates.

it is plausible that the additional cognitive deficits associated with chronic cannabis use have deleterious psychosocial ramifications. For example, our study found that cannabis users were twice as likely to be unemployed than nonusers. While the reasons for this are not clear, an association between impaired cognitive performance and unemployment in patients with MS has been reported,²⁶ thereby suggesting a putative link with our cannabis findings.

To date, the clinical trials literature on the effects of cannabis on cognition in patients with MS is sparse, largely limited to synthetic cannabis derivatives or cannabis-based extracts, with measures of cognition confined to secondary analysis. Results are equivocal, with deficits in long-term memory storage reported by one study¹ contrasting with an absence of deleterious cognitive problems associated with cannabinoids reported by others.^{4,27} The discrepancy between these negative findings and our results may be attributable to differences in pharmacokinetics between the various forms of cannabis and their routes of administration. Oral administration of cannabi-

noids has a slower onset of action, more erratic patterns of absorption, and lower peak concentration compared to inhaled cannabis, which allows for better absorption than oral THC.

The results of our study are consistent with data from an earlier pilot study that revealed that patients with MS who smoked cannabis performed significantly more poorly than cannabis-naïve patients on a test of information processing speed.⁷ While informative, the earlier study had a small sample size (10 cannabis users), a limited neuropsychological battery, and the absence of urinalysis confirming cannabis use. Our present study, by virtue of a more robust methodology, extends these earlier results and links smoked or ingested cannabis to more extensive cognitive deficits.

The paucity of cognitive data pertaining to the use of inhaled cannabis in patients with MS contrasts with a much larger literature obtained from general population studies. Results here have varied according to the timing of the neuropsychological inquiry. For example, there is a consistent body of evidence showing that individuals who are acutely intoxicated

display impaired memory, slowed information processing speed, and poor attention.^{28,29} What defines acute intoxication in the literature is somewhat arbitrary, with studies using 4 to 24 hours as the cutoff period.^{28,29} Of note, however, is that pharmacokinetic studies have shown that the acute cognitive effects of cannabis attributable to the initial rapid rise in serum THC begin tapering off 3 to 5 hours after consumption.^{30,31} Given that we did not want to test cognition in patients who were acutely intoxicated, we set a time frame for psychometric testing as greater than 12 hours following the last inhalation or ingestion of cannabis. The literature from the general population suggests, with few exceptions,³² that there are residual, adverse cognitive difficulties extending beyond this period.³³⁻³⁵ Our finding in the cannabis users replicates this picture and points toward the detrimental effects of cannabis persisting beyond intoxication. While it is likely that these persistent deficits are due to the residual effects of the drug itself, whether and to what extent withdrawal effects following a short period of abstinence contribute as well cannot be ascertained from our data. Notably, we did not find an association between cognitive performance and duration of abstinence (12–24 hours vs greater than 24 hours) in this study.

Cognitive dysfunction in our sample was not associated with the level of cannabinoid metabolites detected in the urine and the age at onset, duration of cannabis use, or abstinence. It is, however, possible that the lack of association may be an artifact of our sample selection where the overwhelming majority of our cannabis users began using the drug in adolescence and in whom urinary levels of metabolites clustered tightly at the upper limits of the range of detection. Our data also diverged from the general population finding of higher rates of psychopathology in cannabis users.³⁶ This pertained both to the lifetime prevalence of these disorders and current indices of emotional distress as captured by the HADS. This result may, in part, be attributed to the already high prevalence of depressive and anxiety disorders associated with MS itself.^{37,38}

A notable cognitive finding from our study was that twice as many cannabis users were rated as globally impaired when compared with the noncannabis users. While our methodology did not address etiologic constructs, fMRI data from patients with MS have consistently shown that in response to a cognitive challenge, ancillary brain activation occurs as a compensatory response to the presence of cerebral pathology.^{39,40} It is therefore tempting to speculate that the deleterious effects of cannabis may be linked to an inhibition of these compensatory responses. In addition, functional imaging findings from the gen-

eral psychiatry literature have demonstrated lower global and prefrontal blood flow in cannabis users even before they are challenged with a cognitive task.⁴⁰ These resting state data suggest that a degree of “background” cerebral compromise may further complicate cognitive functioning.

Our study has limitations. The cross-sectional design limits our ability to establish a cause and effect relationship between cannabis use and greater cognitive dysfunction. It is also important to emphasize that our results are derived from patients who have smoked cannabis on a regular basis, as much as several times per day, for more than 2 decades. These results do not necessarily extend to occasional cannabis use or frequent use for a brief period of time. Indeed, studies of cannabis use in healthy individuals have shown that the cognitive effects of cannabis are dose-dependent, with deficits in cognition primarily observed in heavy cannabis users^{34,35} and those who use cannabis over a long period of time.³⁵ Our study also does not address the reversibility of these cognitive deficits following long-term abstinence from the drug. Finally, our modest sample size introduces a cautionary note.

Our study demonstrates that inhaled or ingested cannabis is associated with adverse effects on cognition following prolonged use. Given the prevalence of cannabis use in patients with MS, further research is needed to replicate these findings in a larger sample and to explore the cerebral underpinnings of how these changes may come about.

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DISCLOSURE

K. Honarmand has received speaker honoraria from EMD Serono, Inc.; and receives/has received support from an Ontario Graduate Scholarship and an MS Society of Canada Research Studentship grant. Dr. Tierney reports no disclosures. Dr. O'Connor serves on scientific advisory boards for Novartis, Sanofi-Aventis, Bayer Schering Pharma, Genentech, Inc., and Roche; has received speaker honoraria from Biogen Idec, Teva Pharmaceutical Industries Ltd., Novartis, and Sanofi-Aventis; has served as a consultant for Biogen Idec, Actelion Pharmaceuticals Ltd, Bayer Schering Pharma, EMD Serono, Inc., Teva Pharmaceutical Industries Ltd., Genentech Inc., and Warburg Pincus; has received research support from Abbott, Bayer Schering Pharma, Novartis, BioMS Medical, Sanofi-Aventis, CIS Pharma, Genmab A/S, Cognosci, Inc., Wyeth, Daiichi Sankyo, and Roche; and serves as the National Scientific and Clinical Advisor to the MS Society of Canada. Dr. Feinstein has served on scientific advisory boards for Merck Serono and Avanir Pharmaceuticals; has received speaker honoraria from Merck Serono, Teva Pharmaceutical Industries Ltd., Bayer Schering Pharma, and Biogen Idec; serves on the editorial boards of *Multiple Sclerosis* and the *African Journal of Psychiatry*; receives publishing royalties for *The Clinical Neuropsychiatry of Multiple Sclerosis* (Cambridge University Press, 2007); serves on the Medical

Advisory Committee for the Multiple Sclerosis Society of Canada; conducts neuropsychiatric evaluation, cognitive testing, brain imaging in neuropsychiatry in his clinical practice (20% effort); and receives research support from Teva Pharmaceutical Industries Ltd., Merck Serono, Canadian Institute of Health Research, and the Multiple Sclerosis Society of Canada.

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REFERENCES

1. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 2005;65:812–819.
2. Freeman RM, Adekanmi O, Waterfield MR, Waterfield AE, Wright D, Zajicek J. The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomized placebo-controlled trial (CAMS-LUTS). *Int Urogynecol J* 2006;17:636–641.
3. UK MS Research Group, Zajicek J, Fox P, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomized placebo-controlled trial. *Lancet* 2003;362:1517–1526.
4. Aragona M, Onesti E, Tomassini V, et al. Psychopathological and cognitive effects of therapeutic cannabinoids in multiple sclerosis: a double-blind, placebo controlled, crossover study. *Clin Neuropharmacol* 2009;32:41–47.
5. Clark AJ, Ware MA, Yazer E, Murray TJ, Lynch ME. Patterns of cannabis use among patients with multiple sclerosis. *Neurology* 2004;62:2098–2100.
6. Martinez-Rodriguez JE, Munteis E, Carreno M, et al. Cannabis use in Spanish patients with multiple sclerosis: Fulfillment of patient expectations? *J Neurol Sci* 2008;273:103–107.
7. Ghaffar O, Feinstein A. Multiple sclerosis and cannabis: a cognitive and psychiatric study. *Neurology* 2008;71:164–169.
8. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis: I: frequency, patterns, and prediction. *Neurology* 1991;41:685–691.
9. Lyon-Caen O, Jouvent R, Hauser S, et al. Cognitive function in recent-onset demyelinating diseases. *Arch Neurol* 1986;43:1138–1141.
10. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. *Ann Neurol* 2001;50:121–127.
11. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). *Neurology* 1983;33:1444–1452.
12. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Association; 1994.
13. Honarmand K, Feinstein A. Validation of the Hospital Anxiety and Depression Scale for use with multiple sclerosis patients. *Mult Scler* 2009;15:1518–1524.
14. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schleich WF. Measuring the functional impact of fatigue: initial validation of the Fatigue Impact Scale. *Clin Infect Dis* 1994;18:S79–S83.
15. Nelson HE. *National Adult Reading Test (NART): test manual*. Windsor, UK: NFER Nelson; 1982.
16. Benedict RHB, Fischer JS, Archibald CJ, et al. Minimal neuropsychological assessment of MS patients: a consensus approach. *Clin Neuropsychol* 2004;16:381–397.
17. Benedict RHB, Cookfair D, Gavett R, et al. Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *J Int Neuropsychol Soc* 2006;12:549–558.
18. Delis DC, Kramer JH, Kaplan E, Ober BA. *California Verbal Learning Test Manual, Adult Version*, 2nd ed. San Antonio, TX: Psychological Corporation; 2000.
19. Benedict RHB. *Brief Visuospatial Memory Test—Revised: Professional Manual*. Odessa, FL: Psychological Assessment Resources, Inc.; 1997.
20. Benton AL, Sivan AB, Hamsher K, Varney NR, Spreen O. *Contributions to Neuropsychological Assessment*, 2nd ed. New York: Oxford University Press; 1994.
21. Benton AL, Hamsher K. *Multilingual Aphasia Examination Manual*. Iowa City: University of Iowa; 1989.
22. Delis DC, Kaplan E, Kramer JH. *Delis-Kaplan Executive Function System*. San Antonio, TX: Psychological Corporation; 2001.
23. Gronwall DMA. Paced Auditory Serial Addition Test: a measure of recovery from concussion. *Percept Mot Skills* 1977;44:367–373.
24. Smith A. *Symbol Digit Modalities Test Manual*. Los Angeles: Western Psychological Services; 1973.
25. Benito-Leon J, Morales JM, Rivera-Navarro J. Health-related quality of life and its relationship to cognitive and emotional functioning in multiple sclerosis patients. *Eur J Neurol* 2002;9:497–502.
26. Beatty WW, Blanco CR, Wilbanks SI, Paul RH. Demographic, clinical, and cognitive characteristics of multiple sclerosis patients who continue to work. *Neurorehabil Neural Repair* 1995;9:167–173.
27. Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler* 2004;10:434–441.
28. Leirer VO, Yesavage JA, Morrow DG. Marijuana carry-over effects on aircraft pilot performance. *Aviat Space Environ Med* 1991;62:221–227.
29. Barnett G, Licko V, Thompson T. Behavioral pharmacokinetics of marijuana. *Psychopharmacology* 1985;85:51–56.
30. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinetics* 2003;42:327–360.
31. Berghaus G, Krüger HP, Vollrath M. Beeinträchtigung fahrrelevanter Leistungen nach Rauchen von Cannabis und nach Alkoholkonsum: Eine vergleichende Metaanalyse experimenteller Studien [Impairment of driving-related performance after smoking of cannabis and of alcohol use: a comparative meta-analysis of experimental studies]. In: Berghaus G, Krüger HP, eds. *Cannabis im Straßenverkehr [Cannabis and Driving]*. Stuttgart: Gustav Fisher Verlag; 1998:99–112.
32. Carlin AS, Trupin EW. Effect of long-term chronic marijuana use on neuropsychological functioning. *Int J Addict* 1977;12:617–624.
33. Pope HG, Gruber AJ, Yurgelun-Todd D. Residual neuropsychological effects of cannabis. *Curr Psychiatry Rep* 2001;3:507–512.
34. Fried PA, Watkinson B, Gray R. Neurocognitive consequences of marijuana: a comparison with pre-drug performance. *Neurotoxicol Teratol* 2005;27:231–239.

35. Solowij N, Michie PT, Fox AM. Differential impairments of selective attention due to frequency and duration of cannabis use. *Biol Psychiatry* 1995b;37:731–739.
36. Cheung JTW, Mann RE, Lalomiteanu A, et al. Anxiety and mood disorders and cannabis use. *Am J Drug Alcohol Abuse* 2010;36:118–122.
37. Minden SL, Schiffer RB. Affective disorders in multiple sclerosis: review and recommendations for clinical research. *Arch Neurol* 1990;47:98–104.
38. Korostil M, Feinstein A. Anxiety disorders and their clinical correlates in multiple sclerosis patients. *Mult Scler* 2007;13:67–72.
39. Forn C, Barros-Loscertales A, Escudero J, et al. Compensatory activations in patients with multiple sclerosis during preserved performance on the auditory N-back task. *Hum Brain Mapp* 2007;28:424–430.
40. Martin-Santos R, Fagundo AB, Crippa JA, et al. Neuroimaging in cannabis use: a systematic review of the literature. *Psychol Med* 2010;40:383–398.

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Cannabis use in patients with multiple sclerosis

MS Chong^{1,4}, K Wolff², K Wise², C Tanton³, A Winstock² and E Silber¹

Introduction Little is known about the extent and patterns of cannabis use in people with multiple sclerosis (MS).

Methods MS patients attending neurology outpatient clinics at two hospitals in London and one in Kent, UK completed a questionnaire.

Results Questionnaires were completed by 254/337 (75%) MS patients. Forty-three per cent had used cannabis at some stage (ever users). Of these, 68% (75/110) had used cannabis to alleviate symptoms of MS (MS-related cannabis use). Forty-six (18%) had used cannabis in the last month (current users), of whom 12% (31/254) had used it for symptom relief. Being married or having a long-term partner, tobacco smokers and increasing disability were independent risk factors for MS-related cannabis use. Compared to patients who could walk unaided, cannabis use was more likely in those who were chair-bound (adjusted OR 2.47; 1.10–5.56) or only able to walk with an aid (adjusted OR 1.56; 0.90–3.60). Pain and spasms were common reasons for cannabis use. Seventy-one per cent of individuals who had never used cannabis said they would try the drug if it were available on prescription.

Conclusion A large proportion of MS patients had tried cannabis for symptom control, however current use was small. A subgroup with greater disability appears to derive some symptomatic benefit. *Multiple Sclerosis* 2006; 12: 646–651. www.sagepub.co.uk

Key words: addiction; cannabis; multiple sclerosis; pain; spasticity

Introduction

Multiple sclerosis (MS) is the most common cause of neurological disability affecting young adults in the UK. Drug therapies for MS include steroids for acute relapses and disease-modifying agents, however symptom control remains the cornerstone of management. Conventional drug therapies have limited benefit in alleviating symptoms, often because of adverse effects, leading a number of patients with MS to use alternative therapies. Cannabis was legally prescribed in the UK until it was reclassified as a Schedule 1 drug within the 1971 Misuse of Drugs Act. In spite of this, anecdotal evidence suggests that many patients continue to use cannabis illegally for medicinal purposes.

The medical use of cannabis is the subject of medical research and public debate [1,2]. A recent report by the House of Lords Select Committee

recommended that cannabis be reclassified as a Schedule 2 drug, enabling medical prescription. Cannabinoids have been purported to alleviate a variety of MS-related symptoms including spasticity, pain, tremor and bladder dysfunction [3]. Interest in the potential therapeutic uses in MS had resulted in The Medical Research Council funding a national placebo-controlled trial to assess the efficacy of synthetic Δ^9 tetrahydrocannabinol (THC) and cannabis extract for alleviating MS symptoms [4].

Despite limited evidence of efficacy, it was our impression that many MS patients use cannabis for medicinal purposes. There have been anecdotal reports where people with MS describe benefits from the drug and a limited number of studies have systematically tried to address the extent, reasons for and patterns of use in a variety of neurological conditions, including MS [5–11]. We

¹ Department of Neurology, Kings College Hospital NHS Trust, London, UK

² National Addictions Centre, Institute of Psychiatry, London, UK

³ The London School of Hygiene and Tropical Medicine, London, UK

⁴ The Medway Hospital NHS Trust, Gillingham, UK

Author for correspondence: Eli Silber, Department of Neurology, 9th floor Ruskin Wing, Kings College Hospital, London SE5 9AZ, UK. E-mail: esilber@doctors.org.uk

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aimed to assess the extent and patterns of cannabis use amongst MS patients in South East London and surroundings. We surveyed MS patients to determine whether there are demographic, behavioural and MS-disability-related factors associated with the medicinal use of cannabis. We also report the perceived benefits and adverse effects of cannabis use.

Methods

Patients with a diagnosis of MS known to the Neurology Departments of Kings College Hospital and the Queen Elizabeth Hospitals in South London and The Medway Hospital in Kent were recruited. Patients under 18 years of age, those with severe mental health problems and those unwilling or unable to give consent were excluded. Information was collected through a self-report questionnaire, which was developed after consultation with and piloting amongst one of the local MS patient support groups. The questionnaire comprised a number of components: (a) demographic details, (b) MS history including disease duration, and disability using the Guy's Neurological Disability Scale [12], (c) current and previous cannabis and other recreational drug use, and (d) subjects were asked about current symptoms using a list derived from clinical experience and patient reports; for each symptom they were asked whether cannabis had been used to try to relieve this and its perceived efficacy.

Subjects who had used cannabis at least once were defined as 'ever users'. Those who were using cannabis at least once a month at the time of the survey were defined as 'current users'. 'MS-related cannabis use' was defined as those individuals who reported that they had (1) not used cannabis before developing MS and that they had started because of MS or (2) those who would not use cannabis if they did not have MS.

Data were entered into SPSS and analysed using STATA (Stata Corporation Texas). Those who completed questionnaires were compared to 'non-responders'. Comparison was made between MS-related users and the rest of the group (non-users and recreational users) and possible risk factors for MS-related cannabis use were determined. Odds ratios (ORs) and 95% confidence intervals (95% CIs) for MS-related cannabis use were calculated using logistic regression.

Results

A response rate of 75% (254/337) was achieved with higher completion among women (79% versus

66%; $P = 0.01$). Amongst men, there was a tendency for a lower response rate in those aged less than 50 years compared to those aged 50 or older ($P = 0.08$).

Characteristics of patients included in the study are shown in Table 1. The median age was 49 years and one-quarter were male. Sixty-five per cent were non-smokers and the majority (66%) drank alcohol within national recommended limits (21 units/week for males and 14 units for females). Nearly 70% of those who completed the questionnaire were either married or cohabiting with a partner and 40% of households had children living at home. MS was diagnosed within the last five years in 34%; between 5 and 15 years ago in 40%; and > 15 years ago in 23% of patients. In terms of lower-limb disability, 29% were able to walk independently, 45% required an aid to walk and 25% required a wheelchair for at least part of the day. When asked to rate their disability, 28% classified themselves as having no or mild disability, 59% reported moderate disability and 12% severe disability. Fifty-two per cent were unable to work or were medically retired.

One hundred and ten subjects (43%) reported having used cannabis at least once in their lifetime (ever users). Amongst 'ever users' (excluding an individual who only used cannabis in a trial), first cannabis use was split fairly evenly before and after the diagnosis of MS. Of the 59 individuals who used cannabis for the first time after diagnosis, 90% reported starting because of their MS. Forty-six (18%) subjects were using cannabis at the time of the survey (current-users, Table 2) and 12% (31/247) reported using cannabis in an attempt to alleviate MS symptoms.

Seventy-five patients (30%) reported cannabis use to attempt to alleviate MS symptoms (MS-related users). The symptoms for which cannabis was used and its perceived effect are shown in Table 3. The most commonly cited symptoms for cannabis use were pain and spasms (>80%) and the majority of persons using it for these symptoms reported benefit. Seventy-one per cent of individuals who had never used cannabis stated that they would try the drug if it were legal or available on prescription.

Comparison of MS-related cannabis users with the rest of the group (Table 1) showed that they were less likely to be single than married or cohabiting. Whether there were children living at home did not influence the risk of using cannabis. There was a strong association between smoking cigarettes and MS-related cannabis use, but no significant association with alcohol consumption or other illicit drug use. There was no significant geographical variation between the three survey sites with regard to cannabis use.

Table 1 Comparison of risk factors between MS-related cannabis users ($n=75$) and non-MS-related cannabis users ($n=179$)

	Users n (%)	Non-users n (%)	Univariate Ors (95%CI)	P -value
Age group				0.15
<40 years	19 (25.3)	46 (27.1)	1	
40–49 years	16 (21.3)	54 (31.8)	0.72 (0.33–1.55)	
50+ years	40 (53.3)	70 (41.2)	1.38 (0.71–2.68)	
Sex				0.19
Male	23 (30.7)	39 (22.7)	1	
Female	52 (69.3)	133 (77.3)	0.66 (0.36–1.22)	
Ethnicity				0.10
UK White	72 (96.0)	155 (90.1)	1	
Other	3 (4.0)	17 (9.9)	0.38 (0.11–1.34)	
Marital status				0.005
Married/cohabiting	55 (74.3)	115 (69.3)	1	
Divorced/Separated	15 (20.3)	19 (11.5)	1.65 (0.78–3.49)	
Single	4 (5.4)	32 (19.3)	0.26 (0.09–0.78)	
Children at home				0.50
Yes	28 (37.8)	69 (41.3)	1	
No	46 (62.2)	98 (58.7)	1.22 (0.69–2.14)	
Educational level				0.54
≤16 years old	37 (50.7)	79 (48.8)	1	
16–18 years old	23 (31.5)	49 (30.3)	1.00 (0.53–1.88)	
Tertiary education	10 (13.7)	19 (11.7)	1.12 (0.48–2.65)	
Other	3 (4.1)	15 (9.3)	0.43 (0.12–1.57)	
Smoking status				0.001
Non-smoker	37 (49.3)	124 (72.1)	1	
Smoker	38 (50.7)	48 (27.9)	2.65 (1.51–4.65)	
Alcohol consumption				0.36
Non-drinker	22 (31.4)	42 (26.3)	1	
Within recommended limits	46 (65.7)	107 (66.9)	0.82 (0.44–1.53)	
Over recommended limits	2 (2.9)	11 (6.9)	0.35 (0.07–1.71)	
Other illicit drug use				0.27
No	58 (80.6)	145 (86.3)	1	
Yes	14 (19.4)	23 (13.7)	1.52 (0.73–3.16)	
Mobility				0.06
Able to walk unaided	15 (20.0)	57 (33.5)	1	
Able to walk only with aid	36 (48.0)	76 (44.7)	1.80 (0.90–3.60)	
Largely chair-bound	24 (32.0)	37 (21.8)	2.46 (1.15–5.30)	
Self-rated disability				0.05
None/mild	15 (20.0)	54 (32.0)	1	
Moderate/severe	60 (80.0)	115 (68.1)	1.88 (0.98–3.60)	

Non-MS-related cannabis users included non-users and recreational users. All subjects did not complete each question, thus totals do not add up to 254.

The risks of MS-related cannabis use increased with greater physical disability. Use was higher in those who rated their disability as moderate or severe and there was a significant trend to increasing use with greater lower-limb dysfunction (OR 1.56; 95%CI 1.07–2.28; $P_{\text{trend}}=0.02$). The odds of cannabis use were approximately double among those who had upper-limb problems that made them dependent upon others (OR=2.22; 95%CI 1.04–4.32) compared with those with no upper-limb disability. MS-related cannabis use did not correlate with fatigue, mood, cognitive, visual, speech or swallowing problems. There was a tendency to greater use of cannabis amongst those

reporting bowel and sexual dysfunction but these were not statistically significant. Multivariate analysis (Table 4) identified tobacco smoking and marital status as independent risk factors for MS-related cannabis use. There was a tendency to lower-limb disability as a risk factor for cannabis use however this did not reach statistical significance.

The side effects experienced by MS-related cannabis users are shown in Table 5. The most common of these were feeling 'quiet and mellow' (41%), sedated (35%), euphoric ('giggly' 27%), 'lazy' (23%) and increased appetite (29%). Three subjects reported that cannabis made them feel 'paranoid', a

Table 2 Pattern of cannabis consumption in 46 current users

	<i>n</i> (%)
First use before MS diagnosis	
Yes	20 (43.5)
No	26 (56.5)
No. of times cannabis is used in a week	
0–5	28 (60.9)
5–10	6 (13.0)
10–15	2 (4.4)
20+	5 (10.9)
Missing	5 (10.9)
Type of cannabis used	
Hash	23 (50.0)
Herbal	16 (34.8)
Both	3 (6.5)
Missing	4 (8.7)
MS-related use	
Yes	31 (67.4)
No	15 (32.6)

further three said it exacerbated their weakness and one experienced hallucinations. The most frequently expressed concerns raised by MS-related users were that not enough research had been carried out on the medicinal use of cannabis for MS (59%), potential harm from smoking tobacco with cannabis (41%), including effects on their lungs (32%), risk of dependence (31%), interference with other treatments (27%), cognitive effects (25%), effects on mood (21%), financial costs (48%) and possible stigma (25%).

Discussion

Our results raise a number of issues including the extent of cannabis use amongst our subjects, the clinical efficacy of cannabis, the risk factors for MS-related use and possible adverse effects. Almost half of the respondents had tried cannabis at some time and of these 68% were 'MS-related users'. There was

a significant correlation between MS-related cannabis use and disability. The other independent determinants of cannabis use were being married or in a stable relationship and cigarette smoking. Possible reasons for the increased use amongst people who were married or cohabiting include the partner's ability to acquire and prepare the cannabis, particularly in those who are more disabled.

There remains debate as to the clinical efficacy of cannabinoids in the management of MS symptoms. Cannabinoids appear to have benefit in reducing pain in MS [13] and other neuropathic pain syndromes [14], however a meta-analysis has suggested that cannabinoids are not more efficacious than minor opiates in the management of pain [15]. Both the CAMS [4] and an earlier smaller study [16] found no significant improvement in spasticity. In the CAMS study, ambulant subjects on cannabinoids had a significant improvement in walking times and self-rated scores of pain and spasticity. Other controlled trials using cannabinoids in MS have reported improvement in bladder function [17], but not tremor [18].

Despite the limited evidence for clinical efficacy and the fact that the drug remains illegal, almost one-third of our patients with MS had used cannabis in an attempt to alleviate symptoms. In the previous month, 18% had used the drug and in two-thirds of these this was MS-related use. The most common symptoms for cannabis use cited by our subjects were pain and spasticity and a large proportion experienced benefit. Similarly, in a survey of 112 MS patients known to use cannabis in the UK and USA, over 90% reported alleviation of symptoms of spasticity and pain [8]. Of note is that over half of our subjects had used cannabis to treat sleep problems and that 88% found cannabis to be helpful for this symptom. The issue of sleep problems in MS has received relatively little research attention but a recent clinic-based survey in

Table 3 Symptoms experienced by MS-related cannabis users (*n* = 75) and perceived effect

Symptom	Number reporting symptom	Ever tried cannabis to help <i>n</i> (%)	Improves/relieves symptom <i>n</i> (%)
Pain	49	41 (83.7)	31 (75.6)
Limb spasms	46	37 (80.4)	30 (81.1)
Headaches	30	18 (60.0)	10 (55.6)
Anxiety	28	16 (57.1)	10 (62.5)
Sleep problems	47	25 (53.2)	22 (88.0)
Low mood	37	19 (51.4)	11 (57.9)
Difficulty walking	50	20 (40.0)	13 (65.0)
Sexual dysfunction	24	8 (33.3)	5 (62.5)
Concentration problems	29	9 (31.0)	3 (33.3)
Fatigue	48	14 (29.2)	6 (42.9)
Vertigo/dizziness	22	6 (27.3)	5 (83.3)
Visual disturbances	26	7 (26.9)	4 (57.1)
Memory problems	23	6 (26.1)	1 (16.7)
Bladder	34	4 (11.8)	2 (50)

Table 4 Univariate and adjusted ORs for MS-related cannabis use

	Univariate ORs (95%CI)	Adjusted ORs* (95%CI)	P-value
Mobility			0.09
Able to walk unaided	1	1	
Able to walk only with aid	1.81 (0.90–3.66)	1.56 (0.75–3.28)	
Largely chair-bound	2.72 (1.25–5.90)	2.47 (1.10–5.56)	
Smoking status			0.001
Non-smoker	1	1	
Smoker	2.60 (1.47–4.62)	2.69 (1.48–4.90)	
Marital status			0.02
Married	1	1	
Divorced/separated	1.47 (0.69–3.16)	1.27 (0.57–2.82)	
Single	0.27 (0.09–0.79)	0.26 (0.08–0.81)	

*Adjusted for other variables in the table ($n = 232$).

our unit has identified initial, middle and terminal insomnia in approximately half of patients [19]. Cannabis use for sleep was not questioned in most previous studies apart from a recent study in Nova Scotia where sleep problems were relieved in over 90% of cases [9]. Surprisingly, in our survey bladder problems were rarely cited as a reason for cannabis use.

Despite the large amount of media attention given to medicinal cannabis use, other studies have also reported relatively low rates of regular self-medication with cannabis. In a recent survey, 43% of patients had used cannabis, 16% for medical purposes [10], and in another survey 36% had ever used cannabis, and 14% continued to use it for symptom treatment [9]. These results are similar to ours and suggest that despite the largely negative results of the recent well conducted trial of cannabis use for spasticity the drug may be both bene-

ficial and tolerated in a small proportion of patients with symptoms resistant to conventional therapies.

There may be risks of self-medication with a psychoactive substance by people with a neurological illness. Recent work has raised concerns about alcohol and illicit drug use amongst people with MS [20,21]. In our subjects, MS-related cannabis use was not associated with alcohol or other illicit substance misuse, however 15% had used other illicit drugs previously. If anything, there appeared to be an inverse relationship between high levels of alcohol consumption and MS-related cannabis use. On the other hand, cigarette smoking was an independent predictor of cannabis use and a proportion of subjects expressed concern about associated tobacco use. A proportion of MS-related users expressed concerns about the costs of cannabis use. Over 70% of non-users said that they would try cannabis if it were legal or available on prescription. Medical prescribing and other formulations (such as tablets or a spray) may be helpful in addressing both the issues of smoking and the association with illicit drug use.

There is a need for careful dosage induction and monitoring when cannabis is used for therapeutic purposes. A small proportion of our cohort experienced potentially serious adverse effects, including psychiatric symptoms and increasing weakness. The long-term safety of cannabis use is uncertain and some have raised concerns about the risk of developing psychiatric disorders with prolonged cannabinoid use [22].

This study has a number of strengths and weaknesses. Like all self-reported surveys, these data are dependent on veracity and recall, a fact that is especially relevant with illegal and/or stigmatizing behaviour. In contrast to some earlier studies [8], our response rate is relatively high (75%) and may thus be more representative of our population. This study also analysed specific risks for cannabis use, in particular social factors, levels of disability and

Table 5 Side effects reported as moderate or severe experienced by MS-related cannabis users ($n = 75$)

Side effect ($n = 75$)	Moderate/severe No. (%)*
Feeling quiet and mellow	31 (41.3)
Sedating/nodding off	26 (34.7)
Increased appetite	22 (29.3)
Making one giggly	20 (26.7)
Making one feel lazy	17 (22.7)
Feeling hyper and chatty	14 (18.7)
Feeling unreal	8 (10.7)
Loss of balance	2 (2.7)
Confused/forgetful thinking	8 (10.7)
Feeling disconnected	8 (10.7)
Rushing thoughts	5 (6.7)
Speech/swallowing	3 (4.0)
Weakness	3 (4.0)
Loss of appetite	2 (2.7)
Headache	4 (5.3)
Blurred vision	1 (1.3)
Paranoia	3 (4.0)
Hallucinations	1 (1.3)
Nausea	1 (1.3)

the specific symptoms for which cannabis was used and its perceived effects.

This study complements information from controlled trials by providing details of actual cannabis use in a large spectrum of people with MS. It demonstrates a strong relationship between cannabis use and disability and raises concerns about the relationship with tobacco use. Further long-term study is needed prior to the drug being made more widely available. These include dosage, routes of delivery, interaction with other prescription drugs and alcohol as well as the possibility of psychological dependence.

References

1. **Goodin D.** Marijuana and multiple sclerosis. *Lancet Neurol* 2004; **3**: 79–80.
2. **Wingerchuk D.** Cannabis for medical purposes: cultivating science, weeding out the fiction. *Lancet* 2004; **364**: 315–16.
3. **Baker D, Pryce G, Giovannoni G, Thompson AJ.** The therapeutic potential of cannabis. *Lancet Neurol* 2003; **2**: 291–98.
4. **Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A et al.** Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003; **362**: 1517–26.
5. **Gorter RW, Butorac M, Cobian EP, van der Sluis W.** Medical use of cannabis in the Netherlands. *Neurology* 2005; **64**: 917–19.
6. **Schnelle M, Grotenhermen F, Reif M, Gorter RW.** [Results of a standardized survey on the medical use of cannabis products in the German-speaking area]. *Forsch Komplementarmed* 1999; **6**: 28–36.
7. **Ware MA, Adams H, Guy GW.** The medicinal use of cannabis in the UK: results of a nationwide survey. *Int J Clin Pract* 2005; **59**: 291–95.
8. **Consroe P, Musty R, Rein J, Tillery W, Pertwee R.** The perceived effects of smoked cannabis on patients with multiple sclerosis. *Eur Neurol* 1997; **38**: 44–48.
9. **Clark AJ, Ware MA, Yazer E, Murray TJ, Lynch ME.** Patterns of cannabis use among patients with multiple sclerosis. *Neurology* 2004; **62**: 2098–100.
10. **Page SA, Verhoef MJ, Stebbins RA, Metz LM, Levy JC.** Cannabis use as described by people with multiple sclerosis. *Can J Neurol Sci* 2003; **30**: 201–205.
11. **Linassi A, Hader W.** Perceived effects of marijuana use by MS patients in Saskatchewan – a pilot study. *Int J MS Care* 2003; **6**: 139–47.
12. **Sharrack B, Hughes RA.** The Guy's Neurological Disability Scale (GNDS): a new disability measure for multiple sclerosis. *Mult Scler* 1999; **5**: 223–33.
13. **Svendsen Kristina B, Jensen Troels S, Bach Flemming W.** Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ* 2004; **329**: 253.
14. **Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U.** Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. *JAMA* 2003; **290**: 1757–62.
15. **Campbell FA, Tramèr MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ.** Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *BMJ* 2001; **323**: 13–16.
16. **Killestein J, Hoogervorst ELJ, Reif M, Kalkers NF, Van Loenen AC, Staats PG et al.** Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology* 2002; **58**: 1404–407.
17. **Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkley KJ, Fowler CJ.** An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. *Mult Scler* 2004; **10**: 425–33.
18. **Fox P, Bain PG, Glickman S, Carroll C, Zajicek J.** The effect of cannabis on tremor in patients with multiple sclerosis. *Neurology* 2004; **62**: 1105–109.
19. **Stanton B, Barnes F, Silber E.** Sleep and fatigue in multiple sclerosis. *Mult Scler* 2006; in press.
20. **Bombardier CH, Blake KD, Ehde DM, Gibbons LE, Moore D, Kraft GH.** Alcohol and drug abuse among persons with multiple sclerosis. *Mult Scler* 2004; **10**: 35–40.
21. **Quesnel S, Feinstein A.** Multiple sclerosis and alcohol: a study of problem drinking. *Mult Scler* 2004; **10**: 197–201.
22. **Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt Terrie E.** Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ* 2002; **325**: 1212–13.



Cannabis use in Spanish patients with multiple sclerosis: Fulfilment of patients' expectations?

Jose E. Martínez-Rodríguez ^{a,*}, Elvira Munteis ^a, Mar Carreño ^b, Yolanda Blanco ^b,
Jaume Roquer ^a, Sergio Abanades ^c, Francesc Graus ^b, Albert Saiz ^b

^a Neurology Service, Hospital del Mar, Institut Municipal d'Investigació Mèdica (IMIM), Barcelona, Spain

^b Neurology Service and Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Hospital Clínic, Universitat de Barcelona, Barcelona, Spain

^c Pharmacology Research Unit, Human Pharmacology and Clinical Neurosciences Research Group, IMIM, Universitat Autònoma de Barcelona, Barcelona, Spain

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ABSTRACT

Objective: Medicinal use of cannabis in chronic neurological diseases is a controversial topic of medical research and the subject of intense public debate. The aim of the study was to evaluate the prevalence of cannabis use, related factors, and degree of satisfaction in Spanish patients with multiple sclerosis (MS) prior to the establishment of medically supervised use.

Methods: Cross-sectional, questionnaire-based survey provided during routine medical visits to consecutive patients in two university-based neurology clinics.

Results: The questionnaire was returned by 175 MS patients (94.1% response rate). The prevalence of ever-use and medicinal cannabis use were 43% and 17.1%, respectively. At the time of the survey, cannabis was being used by 12.5% (5/45) of recreational and 56.7% (17/30) of medical users ($p < 0.001$). First cannabis consumption was after MS onset in 15 (50%) medicinal users. Clinical improvement was reported by 14 (46.7%) medicinal users. Smoking use, awareness of cannabis potential benefits, pain, higher disability, and lower age were independently associated with the medicinal use of cannabis. Most patients would support a future legalisation of cannabis for the control of their symptoms and were willing to receive cannabis under medical control once legalised (83.4% of never-users, 94.5% of ever-users, $p < 0.05$).

Conclusion: Almost half of our MS patients had tried cannabis at some time. However, medicinal use was low and clinical improvement after cannabis use was only reported by a subset of patients. Overall, MS patients were highly motivated for a future medically controlled use.

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1. Introduction

The limited benefit of current treatments for the relief of symptoms in patients with multiple sclerosis (MS) has led to the search for alternative and untried therapies. The use of cannabis in this setting is a controversial topic of medical research with great public interest [1]. Whereas most studies have noted an improvement of some MS symptoms after cannabis use [2,3], others reported a lack of efficacy or even clinical worsening [4]. However, most authors suggest a benefit of cannabinoids in MS in at least a subset of patients with spasticity, muscle spasms, neuropathic pain, and lower urinary tract symptoms.

In 2001, a proposition to the Spanish administration by the Parliament of Catalonia, an autonomous community in northeastern Spain, in order to legalise the medical use of cannabis was denied, but opened up an intense public debate. Since 2007, an oromucosal

cannabis-based medicine can be prescribed as compassionate medicine for the treatment of spasticity and as a foreign medicine for the treatment of neuropathic pain in MS. The present study was aimed at evaluating the current prevalence and pattern of cannabis use, degree of satisfaction and expectations in MS patients of our community prior to any medically supervised cannabis use.

2. Patients and methods

The study was based on a consecutive series of adult patients with a diagnosis of MS, based on McDonald criteria. Patients were controlled in two MS University Clinics (Hospital del Mar and Hospital Clínic of Barcelona, Spain) and were invited to participate in the survey from September 2006 to May 2007. There were no exclusion criteria with the exception of moderate to severe cognitive impairment. A cross-sectional, questionnaire-based survey with fifty-six detailed questions was provided to consecutive patients during their routine visits in the outpatient clinics. Patients were assessed for the Expanded Disability Status Scale (EDSS), progression index, MSSS (Multiple Sclerosis Severity Score), and the MS form (relapsing–

* Corresponding author. Neurology Service, Hospital del Mar, Institut Municipal d'Investigació Mèdica (IMIM), Passeig Marítim 25–29, 08003 Barcelona, Spain. Tel.: +34 932483235; fax: +34 932483376.

E-mail address: 33029jmr@comb.es (J.E. Martínez-Rodríguez).

Table 1
 Characteristics of MS patients who are medicinal users of cannabis (past and current users) compared to non-medicinal users (non-users and recreational users)

		Non-medicinal use (145)	Medicinal use (30)	p	
Age (y)		43.1 (11.6)	41.6 (9.2)	0.5	
Females (%)		94 (64.8%)	19 (63.3%)	0.9	
Years of education		13.3 (3.8)	13.4 (3.3)	0.9	
Laboral status	Active	88 (60.7%)	12 (40%)	0.076	
	Unemployed	9 (6.2%)	4 (13.3%)		
	Retired	42 (28%)	13 (44.3%)		
	No answer	6 (4.1%)	1 (0.3%)		
Monthly economic incomes	<€ 600	16 (11%)	3 (10%)	0.98	
	€ 600–<€ 1200	50 (34.5%)	11 (36.6%)		
	€ 1200–<€ 1800	25 (17.2%)	5 (16.7%)		
	>€ 1800	28 (19.3%)	5 (16.7%)		
	No answer	26 (18%)	6 (20%)		
Cigarette smoking		43 (29%)	21 (70%)	<0.001	
Alcohol intake		52 (35.8%)	10 (33.3%)	0.8	
Time of evolution (y)		10.4 (8.1)	9.8 (5.8)	0.7	
MS Disability	EDSS	2.9 (2)	4.3 (2.1)	<0.01*	
	Progression index	0.37 (0.3)	0.6 (0.42)	<0.01*	
	MSSS	3.63 (2.47)	5.8 (2.59)	<0.001*	
MS clinical form	Relapsing–remitting	106 (73.1%)	18 (58.6%)	0.28	
	Secondary progressive	30 (20.7%)	19 (34.5%)		
	Primary progressive	9 (6.2%)	3 (6.9%)		
MS complaints	Spasticity	44 (30.3%)	17 (56.7%)	<0.01*	
	Pain	33 (22.7%)	19 (63.3%)	<0.001*	
	Fatigue	111 (76.6%)	29 (96.7%)	<0.05*	
	Nocturnal sleep	57 (39.3%)	17 (56.7%)	0.083	
	Tremor	36 (24.8%)	7 (23.3%)	0.88	
	Anxiety	44 (30.3%)	11 (36.7%)	0.49	
	Muscle spasms	45 (31%)	14 (46.7%)	0.1	
	Depression	39 (26.9%)	16 (53.3%)	<0.01*	
	Anal dysfunction	50 (34.5%)	17 (56.7%)	<0.05*	
	Urinary dysfunction	48 (33.1%)	18 (60%)	<0.01*	
	Sexual dysfunction	43 (29.6%)	13 (43.3%)	0.14	
	Diplopia	20 (13.8%)	5 (16.7%)	0.7	
	Appetite	16 (11%)	6 (20%)	0.19	
	Walking	70 (48.3%)	24 (80%)	<0.01*	
	DMD		102 (70.3%)	21 (70%)	0.97
	Awareness of cannabis potential benefit for MS		84 (57.9%)	26 (86.7%)	<0.01
Prone to legalisation		133 (91.7%)	28 (93.3%)	0.8	
Prone to future supervised medical cannabis use		121 (83.4%)	29 (96.7%)	0.17	
Hamilton Depression Scale		10.78 (6.96)	15.07 (7.5)	<0.01	
Expected future benefit (VAS analysis, mm)		65 (30)	62 (26)	0.65	

Mean (SD). DMD: disease-modifying drugs. *Statistically significant.

remitting, secondary progressive, primary progressive). The questionnaire was completed at home and sent back to the Hospital in a postage-paid envelope. No personal identity data was included in the survey, so anonymity was maintained throughout the analysis. The study was approved by the local ethics committees.

Questions were designed to collect detailed information on demographic data, history of cannabis use and opinions. The questionnaire included the following sections: *Section 1, demographic and disease characteristics*: age, sex, marital status, years of education, employment status, economic incomes, smoking habit and alcohol intake, years of disease evolution, age at disease onset, self-reported MS symptoms (detailed in fourteen symptoms as present or absence), and current treatments. *Section 2, personal history of cannabis use*: previous and current consumption (last month), purpose (recreational/medicinal), age at first use, consumption pattern, frequency, type of cannabis (hashish or marijuana), and source of the drug. Medicinal use of cannabis was defined as any recurrent consumption in order to relieve symptoms related with MS. *Section 3, cannabis for medical use*: evaluation of the cannabis effect on clinical symptoms based on 100-mm visual analogue scale (VAS), reasons for cannabis withdrawal, cannabis adverse effects, and general subjective perceptions after cannabis use. *Section 4, opinion of cannabis and general comments*: awareness of the potential medicinal benefits of cannabis, reasons for non-consumption, opinions on cannabis legalisation, and expectations concerning future medically supervised use measured by VAS. A standard Hamilton rating depression scale was additionally included in the survey to assess any potential

effect of the patients' mood state on their answers. A value ≥ 18 was considered suggestive of moderate depression.

3. Statistical analysis

The sample size was calculated estimating the proportion of MS patients using cannabis for medicinal reasons (12% of MS patients, as previously reported) [5] and an estimated prevalence in our region of 3000 MS patients [6]. A sample of 163 patients was required to provide a 95% confidence interval at the 5% level. Patients were classified as cannabis non-users, recreational users, and medicinal users. Values were expressed as percentage or mean (SD). Categorical variables were analysed using the chi-square test, and parametric and non-parametric variables using *T*-test and Kruskal–Wallis test, respectively. Multivariate analysis evaluated odds ratios (OR) and the resulting 95% confidence intervals (CI) of those variables related with cannabis use reaching a $p < 0.1$ in the univariate analysis. Statistical significance was established at a 0.05 level.

4. Results

One hundred and seventy-five MS patients returned the questionnaire (94.1% response rate). The frequency of cannabis ever-use was 43% (75/175). Recreational use of cannabis was reported by 45 patients (25.7%) and medicinal use by 30 patients (17.1%). At the time of the survey, 5 patients were using cannabis for recreational purposes

(12.5% recreational users) and 17 patients for medicinal purposes (56.7% medicinal users) ($p < 0.001$).

Table 1 shows the demographic and clinical characteristics of medicinal cannabis users. These patients had a considerable degree of disability (mean EDSS 4.2 (2.1)) and more than 50% reported disabling clinical symptoms such as pain, spasticity, fatigue, depression, sphincter dysfunction and walking disturbances. Comparison of medicinal users with non-medicinal users (non-users and recreational users) (Table 1) showed a higher frequency of cigarette smoking, higher EDSS, progression index, MSSS, and Hamilton Scale score in medicinal users ($p < 0.05$). Medicinal cannabis users were also significantly more often retired, smokers, had more progressive forms of the disease, higher EDSS, progression index, MSSS and more depressive

symptoms (Hamilton Scale score 15.1 (7.5) vs. 9.4 (7.3), $p < 0.01$) when compared to recreational users (Table 2).

Medicinal users began cannabis consumption at older ages, and half of them after the onset of MS. Use of own prepared ingested or vapour inhaled cannabis were found only among MS medicinal users ($p < 0.001$), and mainly among patients with no previous history of recreational use. Both recreational and medicinal users consumed marijuana more often than hashish, and usually before evening bedtime whatever the purpose of use. Medicinal users grew their own cannabis more often than recreational users ($p < 0.001$) (Table 2). Cigarette smoking, awareness of cannabis potential benefit, pain, higher EDSS, and lower age were independently associated with medicinal use of cannabis (Table 3).

Table 2
Comparison of MS medicinal cannabis users with recreational users

		Recreational use (n=45)	Medicinal use (n=30)	p	
Age (y)		37.8 (8.7)	41.6 (9.2)	0.079	
Females (%)		29 (64.4%)	19 (63.3%)	0.8	
Years of education		13.2 (3.5)	13.4 (3.3)	0.86	
Laboral status	Active	34 (75.6%)	12 (40%)	<0.05	
	Unemployed	3 (6.7%)	4 (13.3%)		
	Retired	6 (13.3%)	13 (44.3%)		
	No answer	2 (4.4%)	1 (0.3%)		
Monthly economic incomes	<€ 600	2 (4.4%)	3 (10%)	0.69	
	€ 600–<€ 1200	18 (40%)	11 (36.6%)		
	€ 1200–<€ 1800	10 (22.2%)	5 (16.7%)		
	>€ 1800	11 (24.5%)	5 (16.7%)		
	No answer	4 (8.9%)	6 (20%)		
Cigarette Smoking		19 (42.2%)	21 (70%)	<0.05*	
Alcohol intake		25 (55.8%)	10 (33.3%)	0.09	
Time of evolution (y)		8.6 (7.1)	9.8 (5.8)	0.47	
Disability	EDSS	2.19 (1.76)	4.3 (2.1)	<0.001*	
	Progression index	0.31 (0.26)	0.6 (0.42)	<0.01*	
	MSSS	2.71 (1.97)	5.8 (2.59)	<0.001*	
MS clinical form	Relapsing–remitting	39 (86.4%)	18 (58.6%)	<0.05*	
	Secondary progressive	5 (11.4%)	19 (34.5%)		
	Primary progressive	1 (2.2%)	3 (6.9%)		
MS complaints	Spasticity	10 (22.2%)	17 (56.7%)	<0.01*	
	Pain	7 (15.6%)	19 (63.3%)	<0.001*	
	Fatigue	31 (68.9%)	29 (96.7%)	<0.01*	
	Nocturnal sleep	14 (31.1%)	17 (56.7%)	<0.05*	
	Tremor	10 (22.2%)	7 (23.3%)	0.9	
	Anxiety	14 (31.1%)	11 (36.7%)	0.7	
	Muscle spasms	15 (33.3%)	14 (46.7%)	0.29	
	Depression	10 (22.2%)	16 (53.3%)	<0.05*	
	Anal dysfunction	15 (33.3%)	17 (56.7%)	0.056	
	Urinary dysfunction	13 (28.9%)	18 (60%)	<0.01*	
	Sexual dysfunction	15 (33.3%)	13 (43.3%)	0.29	
	Diplopia	4 (8.9%)	5 (16.7%)	0.3	
	Appetite	7 (15.6%)	6 (20%)	0.9	
	Walking	16 (35.6%)	24 (80%)	<0.001*	
	Hamilton Depression Scale		9.4 (7.3)	15.1 (7.5)	<0.01*
	DMD		74.4%	21 (70%)	0.6
Age at first consumption		19.4 (4.5)	28.6 (12.6)	<0.001*	
Current use		5 (11.1%)	17 (56.7%)	<0.001*	
Consumption prior to MS		37 (82.2%)	15 (50%)	<0.01*	
Type of cannabis	Hashish	12 (26.7%)	2 (6.7%)	<0.001*	
	Marijuana	21 (46.6%)	26 (86.7%)		
	Both	12 (26.7%)	2 (6.7%)		
Consumption patterns of cannabis	Smoked	45 (100%)	24 (80%)	<0.001*	
	Ingested	2 (4.4%)	11 (36.7%)		
	Inhaled	0	1 (3.3%)		
Source	Own growing	6 (13.3%)	16 (53.3%)	<0.001*	
	Family/Friend	39 (86.7%)	17 (56.7%)		
	Bought	3 (6.7%)	4 (13.3%)		
	No answer	3 (6.7%)	1 (3.3%)		
Adverse effects		10 (22%)	13 (43.3%)	0.05*	
Cannabis discontinuation		11.4%	56.7%	<0.001*	
Patients reporting symptoms improvement after cannabis		0	14 (46.7%)	<0.001*	
Awareness of cannabis potential benefit for MS		31 (68.9%)	26 (86.7%)	<0.05*	
Prone to legalisation		44 (97.8%)	28 (93.3%)	0.3	
Prone to future supervised medicinal cannabis use		42 (93.3%)	29 (96.7%)	0.55	
Expected future benefit (VAS analysis, mm)		7.1 (2.7)	6.2 (2.6)	0.24	

Mean (SD). DMD: disease-modifying drugs. *Statistically significant.

Table 3
Multivariate analysis of factors related with medicinal use of cannabis in MS patients

	OR	IC 95%	p
Cigarette smoking	10.592	2.775–40.429	0.001*
Awareness of potential benefit	6.612	1.131–33.572	0.036*
Pain	5.204	1.294–20.921	0.02*
EDSS	1.608	1.056–2.448	0.027*
Age	0.93	0.867–0.997	0.041*
Retired	1.265	0.283–5.662	0.76
Hamilton Scale \geq 18	0.587	0.113–3.048	0.53
Spasticity	1.433	0.342–6.015	0.62
Fatigue	1.641	0.152–17.755	0.68
Urinary dysfunction	2.56	0.642–10.202	0.18
Anal dysfunction	1.104	0.276–4.416	0.89
Sleep disturbances	3.551	0.9–14.023	0.071
Muscle spasms	0.815	0.212–3.135	0.77

*Statistically significant.

When MS patients were asked about any symptom amelioration, 14 out of 30 medicinal users (46.7%) reported clinical improvement after cannabis use. The VAS evaluation of self-reported clinical modifications after cannabis medicinal use showed a wide range of improvement that was mainly perceived in sleep disturbances, pain, tremor, and muscle spasms (Table 4). Adverse effects, mainly dry mouth, dizziness, somnolence, and feeling “high”, were reported by 13 medicinal users (43%) and 10 recreational users (22%) ($p=0.05$) (Table 5). Cannabis therapy had to be discontinued at some time by 56.7% of medicinal users due to supply problems (9 patients), adverse effects (6 patients), and lack of efficacy (2 patients). Once suppressed, more than 50% of these patients reported some kind of worsening of MS symptoms. Current medicinal users (17 patients) compared to past medicinal users (13 patients) had significantly more tremor (41% vs. 0%), grew cannabis by their own more often (64.7% vs. 15.4%), and reported higher frequency of clinical improvement after cannabis use (52.9% vs. 15.4%).

Awareness of potential cannabis benefits for the control of MS symptoms was higher among consumers (86.7% of MS patients using cannabis for medicinal use, 68.9% of recreational users, and 52.6% of non-users, $p<0.01$). Reasons for not using cannabis despite the awareness of a potential benefit were concerns about possible adverse effects (40.6%), absence of interest (36.2%), considerations of the drug's illegality (14.5%), and unknown supplies (8.7%). Most MS patients would support a future legalisation of cannabis for the control of their symptoms and were willing to receive cannabis under medical control once legalised (83.4% of never-users of cannabis and 94.5% of ever-users, $p<0.05$) (Tables 1 and 2). Most arguments for denying a future supervised use of cannabis were considerations about the illegality of the drug and concerns about possible adverse effects. The

Table 4
Perceived effect of medicinal cannabis analyzed by visual analogue scales (VAS)

	n	VAS
Nocturnal sleep	14	64.2 (27.2)
Muscle spasms	10	50 (27.8)
Pain	17	50 (20.9)
Tremor	7	49.3 (34.5)
Anxiety	10	47.4 (32.8)
Sexual dysfunction	10	40.6 (42.6)
Spasticity	15	40.5 (21.4)
Fatigue	16	40.3 (25.8)
Depression	14	39.7 (30.6)
Walking	16	34.1 (30.5)
Appetite	6	25.7 (35.2)
Diplopia	8	25.2 (35.7)
Anal dysfunction	8	17.4 (21.9)
Urinary dysfunction	9	16.2 (25.5)

Values are expressed as mean (SD).

Table 5
Side effects reported by medicinal and recreational users

	Recreational use (45)	Medicinal use (30)
Dry mouth	3 (6.7%)	5 (16.7%)
Somnolence	4 (8.9%)	3 (10%)
Dizziness	3 (6.7%)	3 (10%)
High	3 (6.7%)	1 (3.3%)
Headache	0	2
Delirium	0	0
Walking disturbances	1 (2.2%)	1 (3.3%)
Anxiety	2 (4.4%)	1 (3.3%)
Palpitations	3 (6.7%)	0
Nausea	0	1 (3.3%)

expected future benefits assessed by VAS were 62 mm (31) in never-users, 71 mm (27) in recreational users, and 62 mm (26) in medicinal users ($p=0.4$).

5. Discussion

The most common symptoms reported by our MS medicinal users of cannabis were spasticity, pain, fatigue, sleep disturbances, depression, sphincter dysfunctions, and walking disturbances. These results were not unexpected considering the high disability of these patients (mean EDSS, 4.3). However, the only disabling complaint independently associated with medicinal cannabis use was the presence of pain. In addition to the well-known association with cigarette smoking, other factors significantly related to medicinal use in the multivariate analysis were awareness of the potential benefits of cannabis, higher disability measured by the EDSS, and younger age.

A beneficial effect of cannabis on clinical complaints was perceived by 46.7% of medicinal users of cannabis, a value that was also very similar among current medicinal users (52.9%). The VAS analysis showed a wide range of clinical improvements suggesting a considerable variability in patients' response. Although the reduced number of analyzed patients limits the interpretation of our study, the percentage of clinical improvement was very similar to a recently published study assessing patients using long-term medicinal cannabis [7]. A feeling of general improvement might explain why patients continue to use cannabis even after no clinical improvement. Additionally, a placebo effect cannot be excluded in those patients consuming the drug for medicinal purposes. Recreational MS users did not perceive any positive effects on clinical complaints, although they have lower disability than medicinal users.

The prevalence of ever-users (43%) and medicinal users (17.1%) of cannabis in our MS patients was similar to other surveys in Canada, UK, USA, and The Netherlands (ranging from 36 to 43%, and from 12 to 22%, respectively) [5,8–11]. The response rate in our study was very high (95%), thus reducing any possible influence of more motivated patients. In addition, our study also directly evaluated the EDSS, progression index, and MSSS as measures of disability and disease progression. As a result, a more accurate assessment was obtained than the self-reported measurements used in previous surveys. It is noteworthy that most of our MS medicinal cannabis users were older than recreational users and started the cannabis use after disease onset. This result differs from previous reports that suggest that medicinal use usually evolves from a prior recreational use [8,11,12]. This consumption pattern would indicate an active search for the drug as an alternative therapy rather than a modification of prior recreational use.

The most usual cannabis source was by own growing or supplies from a close friend or relative. Our MS patients reported frequent discontinuation of the medicinal cannabis use, often due to difficulties in obtaining the drug. Half of these patients had some kind of clinical worsening after suppression. Current medicinal users reported greater clinical improvement and grew more their own cannabis than past

medicinal users, therefore contributing to the continuation of the therapy due to easier cannabis availability. All these facts may imply that most MS patients using cannabis on their own have a high risk of treatment discontinuation with the subsequent potential worsening of symptoms and, additionally, a higher chance of consumption of non-reliable and uncontrolled products.

The therapeutic properties of cannabinoids in MS have been assessed by several studies [1–3,13,14]. Although improvement of clinical symptoms after cannabis use has only been reported by a subset of MS patients, the potential benefits of cannabis in MS may have received too much emphasis based on the popular knowledge of this substance and patients' opinion, favouring the use of cannabis as an alternative therapy in this disease. Whatever the benefit of cannabinoids in MS and its potential long-term effects [7,15], the overall expectations for medically controlled cannabis are high. Our results suggest that once cannabinoids products are available, the majority of MS patients will be more than willing to use them under medical prescription. Further scientific studies are therefore needed to establish the indications for medically controlled cannabinoids for the management of MS symptoms and to avoid the setbacks of a non-supervised use.

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References

- [1] Zajicek J, Fox P, Sanders H, Wright D, Vickery A, Nunn J, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003;362:1517–26.
- [2] Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 2005;65:812–9.
- [3] Collin C, Davies P, Mutiboko IK, Ratcliffe S. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. *Eur J Neurol* 2007;14:290–6.
- [4] Killestein J, Hoogervorst EL, Reif M, Kalkers NF, Van Loenen AC, Staats PG, et al. Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology* 2002;58:1404–7.
- [5] Chong MS, Wolff K, Wise K, Tanton C, Winstock A, Silber E. Cannabis use in patients with multiple sclerosis. *Mult Scler* 2006;12:646–51.
- [6] Bufill E, Blesa R, Galan I, Dean G. Prevalence of multiple sclerosis in the region of Osona, Catalonia, northern Spain. *J Neurol Neurosurg Psychiatry* 1995;58:577–81.
- [7] Wade DT, Makela PM, House H, Bateman C, Robson P. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. *Mult Scler* 2006;12:639–45.
- [8] Clark AJ, Ware MA, Yazer E, Murray TJ, Lynch ME. Patterns of cannabis use among patients with multiple sclerosis. *Neurology* 2004;62:2098–100.
- [9] Consroe P, Musty R, Rein J, Tillery W, Pertwee R. The perceived effects of smoked cannabis on patients with multiple sclerosis. *Eur Neurol* 1997;38:44–8.
- [10] Gorter RW, Butorac M, Cobian EP, van der Sluis W. Medical use of cannabis in the Netherlands. *Neurology* 2005;64:917–9.
- [11] Page SA, Verhoef MJ, Stebbins RA, Metz LM, Levy JC. Cannabis use as described by people with multiple sclerosis. *Can J Neurol Sci* 2003;30:201–5.
- [12] Ware MA, Adams H, Guy GW. The medical use of cannabis in the UK: results of a nationwide survey. *Int J Clin Pract* 2005;59:291–5.
- [13] Arévalo-Martin A, Vela JM, Molina-Holgado E, Borrell J, Guaza C. Therapeutic action of cannabinoids in a murine model of multiple sclerosis. *J Neurosci* 2003;23:2511–6.
- [14] Baker D, Pryce G, Croxford JL, Brown P, Pertwee RG, Huffman JW, et al. Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature* 2000;404:84–7.
- [15] Zajicek JP, Sanders HP, Wright DE, Vickery PJ, Ingram WM, Reilly SM, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. *J Neurol Neurosurg Psychiatry* 2005;76:1664–9.



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Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy

Brenda E. Porter and

Department of Neurology, Stanford University

Catherine Jacobson

Department of Neurology, Stanford University

Abstract

Severe childhood epilepsies are characterized by frequent seizures, neurodevelopmental delays and impaired quality of life. In these treatment-resistant epilepsies, families often seek alternative treatments. This survey explored the use of cannabidiol-enriched cannabis in children with treatment-resistant epilepsy. The survey was presented to parents belonging to a Facebook group dedicated to sharing information about the use of cannabidiol-enriched cannabis to treat their child's seizures. Nineteen responses met the inclusion criteria for the study: a diagnosis of epilepsy and current use of cannabidiol-enriched cannabis. Thirteen children had Dravet syndrome, four had Doose syndrome, and one each had Lennox-Gastaut syndrome and idiopathic epilepsy. The average number of anti-epileptic drugs (AEDs) tried before using cannabidiol-enriched cannabis was 12. Sixteen (84%) of the 19 parents reported a reduction in their child's seizure frequency while taking cannabidiol-enriched cannabis. Of these, two (11%) reported complete seizure freedom, eight (42%) reported a greater than 80% reduction in seizure frequency, and six (32%) reported a 25-60% seizure reduction. Other beneficial effects included increased alertness, better mood and improved sleep. Side effects included drowsiness and fatigue. Our survey shows that parents are using cannabidiol-enriched cannabis as a treatment for children with treatment-resistant epilepsy. Because of the increasing number of states that allow access to medical cannabis, its use will likely be a growing concern for the epilepsy community. Safety and tolerability data for cannabidiol-enriched cannabis use among children is not available. Objective measurements of a standardized preparation of pure cannabidiol are needed to determine whether it is safe, well tolerated and efficacious at controlling seizures in this difficult-to-treat pediatric population.

Keywords

Epilepsy; Pediatric; Intractable; Cannabidiol; Side Effects; Medically refractory seizures; treatment-resistant

Corresponding author: Catherine Jacobson, catherine.jacobson@ucsf.edu.

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Introduction

Childhood epilepsies beginning in the first few years of life are frequently characterized by seizures that are resistant to available treatments, including anti-epileptic drugs (AEDs), the ketogenic diet, high doses of steroids and surgery [1]. A high seizure burden in early childhood likely contributes to the severe cognitive, behavioral and motor delays common in these children [2].

When indicated treatments fail to control their child's seizures, some parents turn to alternative treatments. One of these alternative treatments is cannabidiol-enriched cannabis. The cannabis plant contains approximately 80 cannabinoids of which cannabidiol and Δ^9 -tetrahydrocannabinol (THC) are the two most abundant [3,4].

Cannabidiol and THC exert very different physiological effects. Most importantly, cannabidiol is not psychoactive. In recent years, medical uses of cannabis have focused on cannabidiol, both because of its non-psychoactive nature and because it shows promise in treating disease [5]. However, in states where medical cannabis is legal, cannabidiol is currently only available in whole plant preparations that contain all the components of the cannabis plant, including THC. This poses significant risks when administering cannabidiol-enriched cannabis to epileptic children. First, cannabis use during development has been correlated with deleterious effects on brain development and cognition, primarily due to THC [6,7]. Second, THC can be pro-convulsive in epileptic brains [8].

In contrast to THC, numerous studies conducted over the last 40 years demonstrate anticonvulsant effects of pure cannabidiol in partial and generalized seizure animal models, including acute and kindling models [9,10,11,12,13,14]. In humans, two small double blind, placebo-controlled studies examined pure cannabidiol in adults with treatment-resistant epilepsy. In 1978, Mechoulam et al. randomized nine patients to either 200mg/day of pure cannabidiol or placebo [15]. During the three-month trial, two of four patients treated with cannabidiol became seizure free, whereas seizure frequency was unchanged in the five patients receiving placebo. In a second small clinical trial, 15 adult patients suffering from treatment-resistant secondary generalized epilepsy were randomly divided to placebo or 400mg of pure cannabidiol daily for up to 18 weeks [16]. Among the eight cannabidiol patients, four had a marked reduction and three had a partial reduction in seizures. One of the seven patients on placebo experienced a partial reduction in seizures. The most often reported side effect of pure cannabidiol was drowsiness. No patients reported psychoactive effects. In contrast, an open-label study found that cannabidiol was ineffective in controlling seizures; Ames and Cridland reported that seizure frequency was unchanged in 12 institutionalized patients with uncontrolled seizures receiving 200 mg of pure cannabidiol daily [17].

With the legalization of medical cannabis in an increasing number of states, parents of children with uncontrolled seizures have opted to treat their children's seizures with cannabidiol-enriched cannabis. This trend has produced an online presence of parents describing cannabidiol-enriched cannabis use in children with epilepsy. We asked parents from a Facebook group to anonymously fill out a survey on their experience of giving

cannabidiol-enriched cannabis to their children in order to gain insights into current cannabidiol-enriched cannabis use as an alternative treatment for childhood epilepsy.

Methods

The Stanford University institutional review board judged the study exempt from requiring full review by the board. Study data were collected and managed using REDCap electronic data capture tools hosted at the Stanford Center for Clinical Informatics. REDCap (Research Electronic Data Capture) is a secure web-based application designed to support data capture for research studies [18]. The survey consisted of 24 questions that measured clinical factors, including diagnosis and seizure types, and the parental-reported effect of cannabidiol-enriched cannabis on the child's seizure frequency and side effects. The survey was presented to a Facebook group composed of approximately 150 parents supporting the use of cannabidiol-enriched cannabis to treat seizures in their children with treatment-resistant epilepsy. The survey link was posted and displayed for two weeks, then reposted to the top of the group's page for another two weeks. Twenty parents responded to the survey. Nineteen responses met the inclusion criteria – diagnosis of treatment-resistant epilepsy and cannabidiol-enriched cannabis use – and were included in the analysis. One response was excluded because the child's diagnosis did not include epilepsy.

Because the cannabidiol-enriched cannabis survey results had a large number of patients with Dravet Syndrome and reported mostly positive outcomes for both seizure control and side effects, we wanted to assess parents' response to the same survey questions with a well known and effective treatment for seizures in Dravet syndrome, stiripentol. This would allow us to see if the parents' responses to our seizure burden questions were similar to the results from a clinical trial of stiripentol. In addition, side effects across the two drugs could be compared. To this end, we administered the same survey substituting stiripentol in place of cannabidiol-enriched cannabis. The stiripentol survey was presented to a different Facebook support group composed of parents of children with Dravet Syndrome having approximately 800 members. The stiripentol survey link was also initially posted for two weeks, and reposted to the top of the group's page for two additional weeks. Twenty-two parents responded to the stiripentol survey and all responses were included in analysis. Responses from both surveys were descriptively analyzed.

Results

The results from the cannabidiol-enriched cannabis survey are summarized in Table 1. The children ranged in age from 2 to 16 years. Thirteen children had Dravet syndrome (one of whom had epilepsy in female with mental retardation, EMFR), four children had Doose syndrome, and one each had Lennox-Gastaut syndrome and idiopathic early-onset epilepsy. The children experienced a variety of seizure types including focal, tonic-clonic, myoclonic, atonic and infantile spasms. In all cases, except patient 14 (age 2 years), the children experienced treatment-resistant epilepsy for more than 3 years before trying cannabidiol-enriched cannabis. The 2 year old had experienced intractable seizures for 16 months before trying cannabidiol-enriched cannabis. The children had unsuccessfully tried an average of 12 other AEDs before their parents began cannabidiol-enriched cannabis treatment. The

doses of cannabidiol the parents reported providing ranged from less than 0.5 mg/kg/day to 28.6 mg/kg/day. The doses of THC contained within those samples were reported to range from 0 to 0.8mg/kg/day. To obtain dosage information, parents reported having their preparations tested at commercial medical cannabis testing facilities. Seizure frequency before administering cannabidiol-enriched cannabis ranged from 2 per week to 250 per day. The duration of cannabidiol-enriched cannabis administration ranged from two weeks to over one year. Sixteen (84%) of the 19 parents reported a reduction in their child's seizure frequency. Two parents reported that their child became seizure-free after more than 4 months of cannabidiol-enriched cannabis use. Of the remaining 14 parents reporting a change in seizure frequency, 8 reported a greater than 80% reduction in seizure frequency, three reported a greater than 50% seizure frequency reduction and three reported a greater than 25% seizure frequency reduction. Three parents reported no change. Twelve parents weaned their child from another AED after starting cannabidiol-enriched cannabis treatment (see Table 1).

Beneficial effects of cannabidiol-enriched cannabis other than reduced seizures included better mood (15/19, 79%), increased alertness (14/19, 74%), better sleep (13/19, 68%) and decreased self-stimulation (6/19, 32%). Negative side effects included drowsiness (7/19, 37%) and fatigue (3/19, 16%) (Table 2). Side effects reported while taking other AEDs included rash, vomiting, irritability, dizziness, confusion and aggressive behavior; none were reported with the use of cannabidiol-enriched cannabis.

To understand if our questions might produce results similar to clinical trial results, we asked for responses to an identical survey replacing cannabidiol-enriched cannabis with another AED in use for Dravet syndrome. We surveyed parents on a Facebook group about stiripentol, which is approved only in Europe (though Americans can obtain it). We asked these parents to report how stiripentol affects their child's seizure frequency as well as which side effects were evident on the drug. Fifteen of the 22 (68%) parents reported that stiripentol reduced their child's seizure frequency. Four parents reported a substantial increase in seizure frequency, while three parents reported no change. Common negative side effects reported on stiripentol included appetite decrease (5/22, 23%), weight loss (6/22, 27%), insomnia (4/22, 18%) and increased self-stimulation (3/22, 14%). The reports in response to our survey are consistent with published data on the effects of stiripentol in children with Dravet syndrome [19], and support that our survey questions identify seizure and side effects similar to clinical trial results.

Discussion

Summary

We found that parents of children with severe treatment-resistant epilepsies are using cannabidiol-enriched cannabis to treat their child's epilepsy. Parents report a high rate of success in reducing seizure frequency with this treatment. Cannabidiol-enriched cannabis appears to be behaviorally well tolerated with some positive side effects not commonly associated with other AEDs. There are, of course, multiple limitations of an anonymous parental survey. We cannot verify the doses or the children's response to the cannabidiol-enriched cannabis. We approached a group of parents who have an ongoing interest in using

cannabidiol-enriched cannabis for their children's seizures which likely selected for positive outcomes. Nonetheless, the overall positive results on seizure control in a medically refractory group of childhood epilepsies suggest further studies of cannabidiol are warranted.

Parents report reduced seizures

The report of reduced seizure burden in the population that we surveyed is surprising. The children comprised a highly refractory epilepsy population with the majority having Dravet syndrome, a severe form of childhood epilepsy that often does not respond to available treatments, including AEDs, the ketogenic diet and the vagus nerve stimulator [1]. The children had failed to respond to an average of 12 AEDs prior to the use of cannabidiol-enriched cannabis. The children experienced various seizure types and the parental reports suggest that cannabidiol-enriched cannabis may have efficacy for diverse seizures. The limited size of our survey and small representation of syndromes other than Dravet does not provide additional guidance on what epilepsy types to move forward with in clinical trials. It is important to note, however, that the diagnoses and seizure types reported in this anonymous survey could not be validated by an experienced clinician.

Parents report favorable side effects profile

Quality of life surveys show that adverse effects of AEDs have as much of an impact on the patient's ability to enjoy life as the seizures themselves [20]. Our survey reports that cannabidiol-enriched cannabis is behaviorally well tolerated and may have beneficial effects on cognition and mood. Many parents reported that their children experienced better sleep, increased alertness, and better mood while taking cannabidiol-enriched cannabis. These beneficial side effects are rarely reported with pediatric use of other AEDs [21]. Additionally, many negative side effects commonly associated with AEDs, such as irritability, insomnia and aggressive behavior were notably absent from the parent reports on cannabidiol-enriched cannabis. Because of the apparent efficacy of cannabidiol-enriched cannabis, 12 parents reported weaning their child from other AEDs, thereby further increasing the child's quality of life by removing negative side effects associated with those other AEDs.

Bias Issues

We recognize that this survey has multiple biases that prevent us from making strong conclusions about the overall efficacy of cannabidiol-enriched cannabis in pediatric epilepsy. The positive reports on seizure control and side effects prompted us to investigate whether the wording of the questions produced a strong positive bias. We conducted an additional survey, using the same questions, of parents using stiripentol, a drug that is approved for treatment of Dravet syndrome in Europe. Our results from the stiripentol survey are consistent with published studies on the efficacy and tolerability of stiripentol [19]. Because the answers to the stiripentol survey match the published data on stiripentol's effects, it is unlikely that the wording of the survey questions was inherently biased. Still, there remains the bias of subject selection, in that the parents involved in the Facebook group were proponents of using cannabidiol-enriched cannabis for their children.

Use of medical cannabis poses risks

The new trend of medical cannabis use in children poses risks due to a lack of standardization and regulation, imprecise dosing and possible adverse side effects and medication interactions. A lack of regulation and standardization in the medical cannabis industry results in products that are of questionable quality and composition. Most parents reported using cannabis extracts, either purchased from a dispensary, or directly from a medical cannabis grower. Cannabis extracts are often inaccurately labeled and can contain highly variable levels of cannabidiol and THC. These extracts could also contain contaminants, such as fungus and pesticides, which may cause long-term organ damage. Further, while published reports on pure cannabidiol in animal models, as well as in humans with epilepsy, have demonstrated an anticonvulsant effect of cannabidiol, the data on THC's role in epilepsy is conflicting. In some cases, THC has been shown to be pro-convulsive [22]. Furthermore, animal studies have demonstrated that removal of THC from epileptic animals treated with THC can lead to hyperexcitability [8,22].

Future Directions

Because parents are increasingly using artisanal preparations of cannabidiol-enriched cannabis in an attempt to reduce the child's seizure burden, it is critical to obtain more data about the safety and efficacy of cannabidiol. These poorly regulated preparations may not represent the potential benefits and risks of pure cannabidiol. Formal studies to determine safety, optimal dosing, tolerability and efficacy of a standardized cannabidiol preparation in different populations of children and adults with epilepsy will provide the data necessary to determine whether cannabidiol has a place in epilepsy treatment.

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References

1. Wheless JW. Managing severe epilepsy syndromes of early childhood. *Journal of child neurology*. 2009; 24:24S–32S. quiz 33S–26S. [PubMed: 19666880]
2. McTague A, Cross JH. Treatment of epileptic encephalopathies. *CNS Drugs*. 2013; 27:175–184. [PubMed: 23397290]
3. Mechoulam R, Shani A, Edery H, Grunfeld Y. Chemical basis of hashish activity. *Science*. 1970; 169:611–612. [PubMed: 4987683]
4. Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychoactive plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends in pharmacological sciences*. 2009; 30:515–527. [PubMed: 19729208]
5. Zuairi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Revista brasileira de psiquiatria*. 2008; 30:271–280. [PubMed: 18833429]
6. Meier MH, Caspi A, Ambler A, Harrington H, Houts R, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proceedings of the National Academy of Sciences of the United States of America*. 2012; 109:E2657–2664. [PubMed: 22927402]

7. D'Souza DC, Sewell RA, Ranganathan M. Cannabis and psychosis/schizophrenia: human studies. *European archives of psychiatry and clinical neuroscience*. 2009; 259:413–431. [PubMed: 19609589]
8. Karler R, Turkanis SA. Subacute cannabinoid treatment: anticonvulsant activity and withdrawal excitability in mice. *British journal of pharmacology*. 1980; 68:479–484. [PubMed: 6301593]
9. Izquierdo I, Orsingher OA, Berardi AC. Effect of cannabidiol and of other cannabis sativa compounds on hippocampal seizure discharges. *Psychopharmacologia*. 1973; 28:95–102. [PubMed: 4714680]
10. Izquierdo I, Tannhauser M. Letter: The effect of cannabidiol on maximal electroshock seizures in rats. *The Journal of pharmacy and pharmacology*. 1973; 25:916–917. [PubMed: 4149660]
11. Cox B, ten Ham M, Loskota WJ, Lomax P. The anticonvulsant activity of cannabinoids in seizure sensitive gerbils. *Proceedings of the Western Pharmacology Society*. 1975; 18:154–157. [PubMed: 1178662]
12. Consroe P, Benedito MA, Leite JR, Carlini EA, Mechoulam R. Effects of cannabidiol on behavioral seizures caused by convulsant drugs or current in mice. *European journal of pharmacology*. 1982; 83:293–298. [PubMed: 6129147]
13. Jones NA, Hill AJ, Smith I, Bevan SA, Williams CM, et al. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. *The Journal of pharmacology and experimental therapeutics*. 2010; 332:569–577. [PubMed: 19906779]
14. Jones NA, Glyn SE, Akiyama S, Hill TD, Hill AJ, et al. Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures. *Seizure: the journal of the British Epilepsy Association*. 2012; 21:344–352. [PubMed: 22520455]
15. Mechoulam R, Carlini EA. Toward drugs derived from cannabis. *Die Naturwissenschaften*. 1978; 65:174–179. [PubMed: 351429]
16. Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel C, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology*. 1980; 21:175–185. [PubMed: 7413719]
17. Ames FR, Cridland S. Anticonvulsant effect of cannabidiol. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde*. 1986; 69:14. [PubMed: 3941934]
18. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, et al. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of biomedical informatics*. 2009; 42:377–381. [PubMed: 18929686]
19. Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, et al. STICLO study group. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. *Lancet*. 2000; 356:1638–1642. [PubMed: 11089822]
20. Wheless JW. Intractable epilepsy: A survey of patients and caregivers. *Epilepsy & behavior: E&B*. 2006; 8:756–764.
21. Bourgeois BF. Initiating antiepileptic drug treatment and characteristics of drugs. *Handbook of clinical neurology*. 2013; 111:719–725. [PubMed: 23622219]
22. Consroe P, Martin P, Eisenstein D. Anticonvulsant drug antagonism of delta9tetrahydrocannabinol-induced seizures in rabbits. *Research communications in chemical pathology and pharmacology*. 1977; 16:1–13. [PubMed: 841172]
23. Turkanis SA, Karler R. Excitatory and depressant effects of delta 9-tetrahydrocannabinol and cannabidiol on cortical evoked responses in the conscious rat. *Psychopharmacology*. 1981; 75:294–298. [PubMed: 6275447]

Table 1

Summary of Survey Responses

Patient	Diagnosis	Age & Sex	Age at Seizure Onset	Time on CBD	CBD (mg/kg/day)	THC (mg/kg/day)	Seizures before CBD	Seizures after CBD	Estimated Change in Seizure Frequency	Number of AEDs tried before CBD	AEDs discontinued while on CBD
1	LGS	7y female	<1y	> 1y	?	?	> 100/day	8-10/day	> -80%	8	Banzel, Onfi
2	DS	14y female	<1y	> 4m	14	0.5	5/day	0-1/day	> -80%	12	
3	EMFR	12y female	<1y	2-4m	7	0.5	12/day	0-1/day	> -80%	17	
4	DS	7y male	<1y	> 4m	8	0.25-0.5	50/week	50/week	0	16	
5	DS	6y female	<1y	> 4m	4	0.1-0.25	200-300/week	0-2/week	> -80%	6	Onfi
6	DS	16y female	<1y	> 4m	1-2	0.02-0.1	7/week	4/week	-25%	16	Onfi
7	DS	13y male	<1y	3-4m	4	0.02-0.1	40/week	30/week	-25%	16	Phenobarbital, Depakote
8	DS		<1y	> 4m	?	?	3/week	1-2/week	-50%	14	Klonopin
9	DS	male	<1y	> 4m	3-4	0.04-0.2	100-500/week	1-2/week	> -80%	10	STP, Topamax, Depakote
10	DS		<1y	> 4m	4	0.2-0.4	200-300/week	20-50/week	> -80%	12	STP

Patient	Diagnosis	Age & Sex	Age at Seizure Onset	Time on CBD	CBD (mg/kg/day)	THC (mg/kg/day)	Seizures before CBD	Seizures after CBD	Estimated Change in Seizure Frequency	Number of AEDs tried before CBD	AEDs discontinued while on CBD
11	DS	8y female	<1y	> 1y	?	?	5-10/week	0-3/week	-60%	10	STP, Onfi, Depakote
12	DS	7y female	<1y	> 4m	3-4	0.04-0.2	20+/week	0-10/week	-50%	10	Onfi, Zonagra, Depakote
13	Doose	9y female	<1y	> 4m	10-13	0.5	60-250/day	0	> -80%	15	Lorazepam, Ethosuximide
14	DS	2y male	<1y	> 4m	7	0.08-0.4	2/week	0	> -80%	4	
15	Doose		2-5y	2w	<0.5	0.01-0.05	1-7/week	1-7/week	0	13	
16	Doose	11y male	2-5y	1-2m	6	0.6-0.8	20/week	4/week	> -80%	13	
17	Doose		2-5y	1-2m	6	0	15-20/day	0-3/day	> -80%	14	Steroids
18	Idiopathic	female	1-2y	< 1m	28	0.5-0.7	10/week	8/week	-25%	5	Valproic Acid
19	DS	6y female	<1y	> 4m	1	0.06-0.3	3/week	3/week	0	?	

LGS, Lennox-Gastaut syndrome; DS, Dravet syndrome, EMFR, Epilepsy in females with mental retardation; STP, Stiripentol; y, year; m, month.

Table 2
Reported side effects

	Cannabidiol	Stiripentol	All AEDs
Positive Side Effects			
Better Mood	15/19 (79%)	6/22 (27%)	4/22 (18%)
Increased Alertness	14/19 (74%)	5/22 (23%)	6/22 (27%)
Better Sleep	13/19 (68%)	6/22 (27%)	5/22 (23%)
Decreased Self-stimulation	6/19 (32%)	2/22 (9%)	3/22 (14%)
Negative Side Effects			
Drowsiness	7/19 (37%)	5/22 (23%)	20/22 (91%)
Fatigue	3/19 (16%)	7/22 (32%)	19/22 (86%)
Appetite Decrease	1/19 (5%)	5/22 (23%)	17/22 (77%)
Irritability	--	2/22 (9%)	17/22 (77%)
Insomnia	--	4/22 (18%)	17/22 (77%)
Aggressive Behavior	--	1/22 (5%)	15/22 (68%)
Weight Loss	--	6/22 (27%)	15/22 (68%)
Increased Self-stimulation	--	3/22 (14%)	14/22 (64%)
Appetite Increase	--	2/22 (9%)	10/22 (45%)
Confusion	--	--	9/22 (41%)
Weight Gain	--	1/22 (5%)	9/22 (41%)
Anxiety	--	1/22 (5%)	7/22 (32%)
Nausea	--	2/22 (9%)	6/22 (27%)
Rash	--	--	5/22 (23%)
Vomiting	--	2/22 (9%)	5/22 (23%)
Dizziness	--	--	5/22 (23%)

--, not reported

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Mary Barna Bridgeman, PharmD, BCPS, BCGP; and Daniel T. Abazia, PharmD, BCPS, CPE

INTRODUCTION

Medicinal cannabis, or medicinal marijuana, is a therapy that has garnered much national attention in recent years. Controversies surrounding legal, ethical, and societal implications associated with use; safe administration, packaging, and dispensing; adverse health consequences and deaths attributed to marijuana intoxication; and therapeutic indications based on limited clinical data represent some of the complexities associated with this treatment. Marijuana is currently recognized by the U.S. Drug Enforcement Agency's (DEA's) Comprehensive Drug Abuse Prevention and Control Act (Controlled Substances Act) of 1970 as a Schedule I controlled substance, defined as having a high potential for abuse, no currently accepted medicinal use in treatment in the United States, and a lack of accepted safety data for use of the treatment under medical supervision.¹

Cannabis is the most commonly cultivated, trafficked, and abused illicit drug worldwide; according to the World Health Organization (WHO), marijuana consumption has an annual prevalence rate of approximately 147 million individuals or nearly 2.5% of the global population.² In 2014, approximately 22.2 million Americans 12 years of age or older reported current cannabis use, with 8.4% of this population reporting use within the previous month.^{3,4} General cannabis use, both for recreational and medicinal purposes, has garnered increasing acceptance across the country as evidenced by legislative actions, ballot measures, and public opinion polls; an October 2016 Gallup poll on American's views on legalizing cannabis indicated that 60% of the population surveyed believed the substance should be legalized.⁵ Further, a recent Quinnipiac University poll concluded 54% of American voters surveyed would favor the legalization of cannabis without additional constraints, while 81% of respondents favored legalization of cannabis for medicinal purposes.⁶ Limited data suggest that health care providers also may consider this therapy in certain circumstances.⁷⁻⁹ In the United States, cannabis is approved for medicinal use in 28 states, the District of Columbia, Guam, and Puerto Rico as of January 2017.¹⁰

The use and acceptance of medicinal cannabis continues to evolve, as shown by the growing number of states now permitting use for specific medical indications. The Food and Drug Administration (FDA) has considered how it might support the scientific rigor of medicinal cannabis claims, and the review of public data regarding safety and abuse potential

is ongoing.^{11,12} The purpose of this article is to review the historical significance of the use of medicinal cannabis and to discuss its pharmacology, pharmacokinetics, and select evidence on medicinal uses, as well as to describe the implications of evolving medicinal cannabis regulations and their effects on the acute care hospital setting.

HISTORICAL SIGNIFICANCE

Cannabis is a plant-based, or botanical, product with origins tracing back to the ancient world. Evidence suggesting its use more than 5,000 years ago in what is now Romania has been described extensively.¹³ There is only one direct source of evidence (Δ^6 -tetrahydrocannabinol [Δ^6 -THC] in ashes) that cannabis was first used medicinally around 400 AD.¹⁴ In the U.S., cannabis was widely utilized as a patent medicine during the 19th and early 20th centuries, described in the *United States Pharmacopoeia* for the first time in 1850. Federal restriction of cannabis use and cannabis sale first occurred in 1937 with the passage of the Marihuana Tax Act.^{15,16} Subsequent to the act of 1937, cannabis was dropped from the *United States Pharmacopoeia* in 1942, with legal penalties for possession increasing in 1951 and 1956 with the enactment of the Boggs and Narcotic Control Acts, respectively, and prohibition under federal law occurring with the Controlled Substances Act of 1970.^{1,17,18} Beyond criminalization, these legislative actions contributed to creating limitations on research by restricting procurement of cannabis for academic purposes.

In 1996, California became the first state to permit legal access to and use of botanical cannabis for medicinal purposes under physician supervision with the enactment of the Compassionate Use Act. As previously stated, as of January 1, 2017, 28 states as well as Washington, D.C., Guam, and Puerto Rico will have enacted legislation governing medicinal cannabis sale and distribution; 21 states and the District of Columbia will have decriminalized marijuana and eliminated prohibition for possession of small amounts, while eight states, including Alaska, California, Colorado, Maine, Massachusetts, Nevada, Oregon, and Washington, as well as the District of Columbia, will have legalized use of marijuana for adult recreation.^{10,19}

THE MEDICINAL CANNABIS DEBATE

As a Schedule I controlled substance with no accepted medicinal use, high abuse potential, concerns for dependence, and lack of accepted safety for use under medical supervision—along with a national stigma surrounding the potential harms and implication of cannabis use as a gateway drug to other substances—transitioning from a vilified substance to one with therapeutic merits has been controversial. The *United States Pharmacopoeia* and the FDA have considered the complexities

Dr. Bridgeman is a Clinical Associate Professor at the Ernest Mario School of Pharmacy at Rutgers, the State University of New Jersey, in Piscataway, New Jersey, and an Internal Medicine Clinical Pharmacist at Robert Wood Johnson University Hospital in New Brunswick, New Jersey. Dr. Abazia is a Clinical Assistant Professor at the Ernest Mario School of Pharmacy at Rutgers, the State University of New Jersey, and an Internal Medicine Clinical Pharmacist at Capital Health Regional Medical Center in Trenton, New Jersey.

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of regulating this plant-based therapy, including the numerous compounds and complex interactions between substances in this product, and how it might fit into the current regulatory framework of drugs in United States.^{11,12,17}

The emergence of interest in botanical medicinal cannabis is thought by many to be a collateral effect of the opioid abuse epidemic; public perception surrounding the use of medicinal cannabis suggests that this plant-based therapy is viewed as not much different than a botanical drug product or supplement used for health or relief of symptoms if disease persists. Like some herbal preparations or supplements, however, medicinal cannabis may similarly pose health risks associated with its use, including psychoactive, intoxicating, and impairing effects, which have not been completely elucidated through clinical trials. Proponents argue that there is evidence to support botanical medicinal cannabis in the treatment of a variety of conditions, particularly when symptoms are refractory to other therapies; that beneficial cannabinoids exist, as evidenced by single-entity agents derived from cannabis containing the compounds THC and cannabidiol (CBD); that cannabis is relatively safe, with few deaths reported from use; that therapy is self-titratable by the patient; and that therapy is relatively inexpensive compared with pharmaceutical agents.^{20–22} Opponents of medicinal cannabis use argue, in part, that well-designed randomized trials to confirm benefits and harms are lacking; that it has not been subject to the rigors of the FDA approval process; that standardization in potency or quantity of pharmacologically active constituents is absent; that adverse health effects relate not only to smoking cannabis but to unmasking mental health disorders, impairing coordination, and affecting judgment; that standardization does not exist for product packaging and controls to prevent inadvertent use by minors or pets; that there is a potential for dependence, addiction, and abuse; and that costs pose a potential burden.^{23–25}

Regardless of personal views and perceptions, to deny or disregard the implications of use of this substance on patient health and the infrastructure of the health care system is irresponsible; clinicians must be aware of these implications and informed about how this therapy may influence practice in a variety of health care settings, including acute care.

PHARMACOLOGY

Endocannabinoids (eCBs) and their receptors are found throughout the human body: nervous system, internal organs, connective tissues, glands, and immune cells. The eCB system has a homeostatic role, having been characterized as “eat, sleep, relax, forget, and protect.”²⁶ It is known that eCBs have a role in the pathology of many disorders while also serving a protective function in certain medical conditions.²⁷ It has been proposed that migraine, fibromyalgia, irritable bowel syndrome, and related conditions represent clinical eCB deficiency syndromes (CEDs). Deficiencies in eCB signaling could be also involved in the pathogenesis of depression. In human studies, eCB system deficiencies have been implicated in schizophrenia, multiple sclerosis (MS), Huntington’s disease, Parkinson’s disease, anorexia, chronic motion sickness, and failure to thrive in infants.²⁸

The eCB system represents a microcosm of psychoneuroimmunology or “mind–body” medicine. The eCB system consists of receptors, endogenous ligands, and ligand metabolic

enzymes. A variety of physiological processes occur when cannabinoid receptors are stimulated. Cannabinoid receptor type 1 (CB₁) is the most abundant G-protein–coupled receptor. It is expressed in the central nervous system, with particularly dense expression in (ranked in order): the substantia nigra, globus pallidus, hippocampus, cerebral cortex, putamen, caudate, cerebellum, and amygdala. CB₁ is also expressed in non-neuronal cells, such as adipocytes and hepatocytes, connective and musculoskeletal tissues, and the gonads. CB₂ is principally associated with cells governing immune function, although it may also be expressed in the central nervous system.

The most well-known eCB ligands are N-arachidonylethanolamide (anandamide or AEA) and sn-2-arachidonoylglycerol (2-AG). AEA and 2-AG are released upon demand from cell membrane phospholipid precursors. This “classic” eCB system has expanded with the discovery of secondary receptors, ligands, and ligand metabolic enzymes. For example, AEA, 2-AG, N-arachidonoyl glycine (NAGly), and the phytocannabinoids Δ^9 -THC and CBD may also serve, to different extents, as ligands at GPR55, GPR18, GPR119, and several transient receptor potential ion channels (e.g., TRPV1, TRPV2, TRPA1, TRPM8) that have actions similar to capsaicin.²⁸ The effects of AEA and 2-AG can be enhanced by “entourage compounds” that inhibit their hydrolysis via substrate competition, and thereby prolong their action through synergy and augmentation. Entourage compounds include N-palmitylethanolamide (PEA), N-oleoylethanolamide (SEA), and cis-9-octadecenoamide (OEA or oleamide) and may represent a novel route for molecular regulation of endogenous cannabinoid activity.²⁹

Additional noncannabinoid targets are also linked to cannabis. G-protein–coupled receptors provide noncompetitive inhibition at mu and delta opioid receptors as well as norepinephrine, dopamine, and serotonin. Ligand-gated ion channels create allosteric antagonism at serotonin and nicotinic receptors, and enhance activation of glycine receptors. Inhibition of calcium, potassium, and sodium channels by noncompetitive antagonism occurs at nonspecific ion channels and activation of PPAR α and PPAR γ at the peroxisome proliferator-activated receptors is influenced by AEA.³⁰

THC is known to be the major psychoactive component of cannabis mediated by activation of the CB₁ receptors in the central nervous system; however, this very mechanism limits its use due to untoward adverse effects. It is now accepted that other phytocannabinoids with weak or no psychoactivity have promise as therapeutic agents in humans. The cannabinoid that has sparked the most interest as a nonpsychoactive component is CBD.³¹ Unlike THC, CBD elicits its pharmacological effects without exerting any significant intrinsic activity on CB₁ and CB₂ receptors. Several activities give CBD a high potential for therapeutic use, including antiepileptic, anxiolytic, anti-psychotic, anti-inflammatory, and neuroprotective effects. CBD in combination with THC has received regulatory approvals in several European countries and is under study in registered trials with the FDA. And, some states have passed legislation to allow for the use of majority CBD preparations of cannabis for certain pathological conditions, despite lack of standardization of CBD content and optimal route of administration for effect.³² Specific applications of CBD have recently emerged in pain (chronic and neuropathic), diabetes, cancer, and neuro-

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degenerative diseases, such as Huntington's disease. Animal studies indicate that a high dose of CBD inhibits the effects of lower doses of THC. Moreover, clinical studies suggest that oral or oromucosal CBD may prolong and/or intensify the effects of THC. Finally, preliminary clinical trials suggest that high-dose oral CBD (150–600 mg per day) may exert a therapeutic effect for epilepsy, insomnia, and social anxiety disorder. Nonetheless, such doses of CBD have also been shown to cause sedation.³³

PHARMACOKINETICS AND ADMINISTRATION

The three most common methods of administration are inhalation via smoking, inhalation via vaporization, and ingestion of edible products. The method of administration can impact the onset, intensity, and duration of psychoactive effects; effects on organ systems; and the addictive potential and negative consequences associated with use.³⁴

Cannabinoid pharmacokinetic research has been challenging; low analyte concentrations, rapid and extensive metabolism, and physicochemical characteristics hinder the separation of compounds of interest from biological matrices and from each other. The net effect is lower drug recovery due to adsorption of compounds of interest to multiple surfaces.³⁵ The primary psychoactive constituent of marijuana— Δ^9 -THC—is rapidly transferred from lungs to blood during smoking. In a randomized controlled trial conducted by Huestis and colleagues, THC was detected in plasma immediately after the first inhalation of marijuana smoke, attesting to the efficient absorption of THC from the lungs. THC levels rose rapidly and peaked prior to the end of smoking.³⁶ Although smoking is the most common cannabis administration route, the use of vaporization is increasing rapidly. Vaporization provides effects similar to smoking while reducing exposure to the byproducts of combustion and possible carcinogens and decreasing adverse respiratory syndromes. THC is highly lipophilic, distributing rapidly to highly perfused tissues and later to fat.³⁷ A trial of 11 healthy subjects administered Δ^9 -THC intravenously, by smoking, and by mouth demonstrated that plasma profiles of THC after smoking and intravenous injection were similar, whereas plasma levels after oral doses were low and irregular, indicating slow and erratic absorption. The time courses of plasma concentrations and clinical "high" were of the same order for intravenous injection and smoking, with prompt onset and steady decline over a four-hour period. After oral THC, the onset of clinical effects was slower and lasted longer, but effects occurred at much lower plasma concentrations than they did after the other two methods of administration.³⁸

Cannabinoids are usually inhaled or taken orally; the rectal route, sublingual administration, transdermal delivery, eye drops, and aerosols have been used in only a few studies and are of little relevance in practice today. The pharmacokinetics of THC vary as a function of its route of administration. Inhalation of THC causes a maximum plasma concentration within minutes and psychotropic effects within seconds to a few minutes. These effects reach their maximum after 15 to 30 minutes and taper off within two to three hours. Following oral ingestion, psychotropic effects manifest within 30 to 90 minutes, reach their maximum effect after two to three hours, and last for about four to 12 hours, depending on the dose.³⁹

Within the shifting legal landscape of medical cannabis, different methods of cannabis administration have important public health implications. A survey using data from Qualtrics and Facebook showed that individuals in states with medical cannabis laws had a significantly higher likelihood of ever having used the substance with a history of vaporizing marijuana (odds ratio [OR], 2.04; 99% confidence interval [CI], 1.62–2.58) and a history of oral administration of edible marijuana (OR, 1.78; 99% CI, 1.39–2.26) than those in states without such laws. Longer duration of medical cannabis status and higher dispensary density were also significantly associated with use of vaporized and edible forms of marijuana. Medical cannabis laws are related to state-level patterns of utilization of alternative methods of cannabis administration.³⁴

DRUG INTERACTIONS

Metabolic and pharmacodynamic interactions may exist between medical cannabis and other pharmaceuticals. Quantification of the *in vitro* metabolism of exogenous cannabinoids, including THC, CBD, and cannabidiol (CBN), indicates hepatic cytochrome 450 (CYP450) isoenzymes 2C9 and 3A4 play a significant role in the primary metabolism of THC and CBN, whereas 2C19 and 3A4 and may be responsible for metabolism of CBD.⁴⁰ Limited clinical trials quantifying the effect of the exogenous cannabinoids on the metabolism of other medications exist; however, drug interaction data may be gleaned from the prescribing information from cannabinoid-derived pharmaceutical products such as Sativex (GW Pharmaceuticals, United Kingdom) and dronabinol (Marinol, AbbVie [United States]).^{41,42} Concomitant administration of ketoconazole with oromucosal cannabis extract containing THC and CBD resulted in an increase in the maximum serum concentration and area under the curve for both THC and CBD by 1.2-fold to 1.8-fold and twofold, respectively; coadministration of rifampin is associated with a reduction in THC and CBD levels.^{40,41} In clinical trials, dronabinol use was not associated with clinically significant drug interactions, although additive pharmacodynamic effects are possible when it is coadministered with other agents having similar physiological effects (e.g., sedatives, alcohol, and antihistamines may increase sedation; tricyclic antidepressants, stimulants, and sympathomimetics may increase tachycardia).⁴¹ Additionally, smoking cannabis may increase theophylline metabolism, as is also seen after smoking tobacco.^{40,42}

ADVERSE EFFECTS

Much of what is known about the adverse effects of medicinal cannabis comes from studies of recreational users of marijuana.⁴³ Short-term use of cannabis has led to impaired short-term memory; impaired motor coordination; altered judgment; and paranoia or psychosis at high doses.⁴⁴ Long-term or heavy use of cannabis, especially in individuals who begin using as adolescents, has led to addiction; altered brain development; cognitive impairment; poor educational outcomes (e.g., dropping out of school); and diminished life satisfaction.⁴⁵ Long-term or heavy use of cannabis is also associated with chronic bronchitis and an increased risk of chronic psychosis-related health disorders, including schizophrenia and variants of depression, in persons with a predisposition to

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such disorders.^{46–48} Vascular conditions, including myocardial infarction, stroke, and transient ischemic attack, have also been associated with cannabis use.^{49–51} The use of cannabis for management of symptoms in neurodegenerative diseases, such as Parkinson's, Alzheimer's, and MS, has provided data related to impaired cognition in these individuals.^{52,53}

A systematic review of published trials on the use of medical cannabinoids over a 40-year period was conducted to quantify adverse effects of this therapy.⁵⁴ A total of 31 studies evaluating the use of medicinal cannabis, including 23 randomized controlled trials and eight observational studies, was included. In the randomized trials, the median duration of cannabinoid exposure was two weeks, with a range between eight hours and 12 months. Of patients assigned to active treatment in these trials, a total of 4,779 adverse effects were reported; 96.6% (4,615) of these were not deemed by authors to be serious. The most common serious adverse effects included relapsing MS (9.1%; 15 events), vomiting (9.8%; 16 events), and urinary tract infections (9.1%; 15 events). No significant differences in the rates of serious adverse events between individuals receiving medical cannabis and controls were identified (relative risk, 1.04; 95% CI, 0.78–1.39). The most commonly reported non-serious adverse event was dizziness, with an occurrence rate of 15.5% (714 events) among people exposed to cannabinoids.⁵⁴

Other negative adverse effects reported with acute cannabis use include hyperemesis syndrome, impaired coordination and performance, anxiety, suicidal ideations or tendencies, and psychotic symptoms, whereas chronic effects may include mood disturbances, exacerbation of psychotic disorders, cannabis use disorders, withdrawal syndrome, and neurocognitive impairments, as well as cardiovascular and respiratory conditions.⁵² Long-term studies evaluating adverse effects of chronic medicinal cannabis use are needed to conclusively evaluate the risks when used for an extended period of time.

MEDICINAL USES

Cannabis and cannabinoid agents are widely used to alleviate symptoms or treat disease, but their efficacy for specific indications is not well established. For chronic pain, the analgesic effect remains unclear. A systematic review of randomized controlled trials was conducted examining cannabinoids in the treatment of chronic noncancer pain, including smoked cannabis, oromucosal extracts of cannabis-based medicine, nabilone, dronabinol, and a novel THC analogue.⁵⁵ Pain conditions included neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain. Fifteen of the 18 included trials demonstrated a significant analgesic effect of cannabinoids compared with placebo. Cannabinoid use was generally well tolerated; adverse effects most commonly reported were mild to moderate in severity. Overall, evidence suggests that cannabinoids are safe and moderately effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis.⁵⁵

While there is not enough evidence to suggest routine use of medicinal cannabis for alleviating chemotherapy-related nausea and vomiting by national or international cancer societies, therapeutic agents based on THC (e.g., dronabinol) have been approved for use as an antiemetic in the United States for a number of years. Only recently has the efficacy and safety of

cannabis-based medicines in managing nausea and vomiting due to chemotherapy been evaluated. In a review of 23 randomized, controlled trials, patients who received cannabis-based products experienced less nausea and vomiting than subjects who received placebo.⁵⁶ The proportion of people experiencing nausea and vomiting who received cannabis-based products was similar to those receiving conventional antiemetics. Subjects using cannabis-based products experienced side effects such as “feeling high,” dizziness, sedation, and dysphoria and dropped out of the studies at a higher rate due to adverse effects compared with participants receiving either placebo or conventional antiemetics. In crossover trials in which patients received cannabis-based products and conventional antiemetics, patients preferred the cannabis-based medicines. Cannabis-based medications may be useful for treating chemotherapy-induced nausea and vomiting that responds poorly to conventional antiemetics. However, the trials produced low to moderate quality evidence and reflected chemotherapy agents and antiemetics that were available in the 1980s and 1990s.

With regard to the management of neurological disorders, including epilepsy and MS, a Cochrane review of four clinical trials that included 48 epileptic patients using CBD as an adjunct treatment to other antiepileptic medications concluded that there were no serious adverse effects associated with CBD use but that no reliable conclusions on the efficacy and safety of the therapy can be drawn from this limited evidence.⁵⁷ The American Academy of Neurology (AAN) has issued a Summary of Systematic Reviews for Clinicians that indicates oral cannabis extract is effective for reducing patient-reported spasticity scores and central pain or painful spasms when used for MS.⁵⁸ THC is probably effective for reducing patient-reported spasticity scores but is likely ineffective for reducing objective measures of spasticity at 15 weeks, the AAN found; there is limited evidence to support the use of cannabis extracts for treatment of Huntington's disease, levodopa-induced dyskinesias in patients with Parkinson's disease, or reducing tic severity in Tourette's.⁵⁸

In older patients, medical cannabinoids have shown no efficacy on dyskinesia, breathlessness, and chemotherapy-induced nausea and vomiting. Some evidence has shown that THC might be useful in treatment of anorexia and behavioral symptoms in patients with dementia. The most common adverse events reported during cannabinoid treatment in older adults were sedation-like symptoms.⁵⁹

Despite limited clinical evidence, a number of medical conditions and associated symptoms have been approved by state legislatures as qualifying conditions for medicinal cannabis use. Table 1 contains a summary of medicinal cannabis indications by state, including select disease states and qualifying debilitating medical conditions or symptoms.^{10,60,61} The most common conditions accepted by states that allow medicinal cannabis relate to relief of the symptoms of cancer, glaucoma, human immunodeficiency virus/acquired immunodeficiency syndrome, and MS. A total of 28 states, the District of Columbia, Guam, and Puerto Rico now allow comprehensive public medical marijuana and cannabis programs.¹⁰ The National Conference of State Legislatures uses the following criteria to determine if a program is comprehensive:

1. Protection from criminal penalties for using marijuana for a medical purpose;

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Table 1 Medicinal Cannabis Indications for Use by State^{10,60,61}

Select Medical Conditions and Diseases													
	Alaska	Arizona	Arkansas	California	Colorado	Connecticut	Delaware	District of Columbia	Florida	Hawaii	Illinois	Maine	
Alzheimer's disease		✓	✓	1			✓	1	1		✓	✓	
HIV/AIDS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Amyotrophic lateral sclerosis		✓	✓	1			✓	1	✓		✓	✓	
Cancer	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Inflammatory bowel disease (e.g., Crohn's, ulcerative colitis)		✓	✓	1		✓		1	✓		✓	✓	
Glaucoma	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	
Multiple sclerosis				1		✓		1	✓		✓		
Parkinson's disease				1		✓		1	✓				
Post-traumatic stress disorder		✓	✓	1		✓	✓	1	✓	✓	✓	✓	
Debilitating Medical Conditions or Associated Symptoms													
Cachexia, anorexia, or wasting syndrome	✓	✓	✓	✓	✓	✓	✓	1	1	✓	✓	✓	
Severe or chronic pain	✓	✓	✓	✓	✓		✓ 3	1	1	✓		✓ 3	
Severe or chronic nausea	✓	✓	✓	✓	✓		✓ 3	1	1	✓		✓	
Seizure disorders (e.g., epilepsy)	✓	✓	✓	✓	✓	✓	✓ 3	1	✓	✓		✓	
Skeletal muscle spasticity (e.g., multiple sclerosis)	✓	✓	✓	✓	✓	✓ 3	✓	✓	1	✓	✓	✓	
1 = State law additionally covers any condition where treatment with medical cannabis would be beneficial, according to the patient's physician 2 = State law covers any severe condition refractory to other medical treatment 3 = Additional restrictions on the use for this indication exist in this state 4 = State law requires providers to certify the existence of a qualifying disease and symptom HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome													

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	Maryland	Massachusetts	Michigan	Minnesota	Montana	Nevada	New Hampshire	New Jersey	New Mexico	New York	North Dakota	Ohio	Oregon	Pennsylvania	Rhode Island	Vermont	Washington
	2	1	✓				✓ 4				✓	✓			✓		
	2	✓	✓	✓	✓	✓	✓ 4	✓ 3	✓	✓ 3	✓	✓	✓	✓	✓	✓ 3	✓
	2	✓	✓		✓		✓ 4	✓	✓	✓	✓	✓		✓			
	2	✓	✓	✓ 3	✓	✓	✓ 4	✓ 3	✓	✓ 3	✓	✓	✓	✓	✓	✓ 3	✓
	2	✓	✓	✓	✓		✓ 4	✓	✓	✓	✓	✓		✓			✓ 3
	2	✓	✓	✓	✓	✓	✓ 4	✓ 3	✓		✓	✓	✓	✓	✓		✓ 3
	2	✓			✓		✓ 4	✓	✓	✓		✓		✓		✓ 3	✓
	2	✓					✓ 4		✓	✓ 3		✓		✓			
	2	1	✓	✓	✓	✓			✓		✓	✓	✓	✓	✓		✓

✓ 2	1	✓		✓	✓	✓ 4	✓ 3	✓ 3		✓		✓		✓	✓ 3	✓ 3
✓ 2	1	✓		✓ 3	✓	✓ 3,4		✓ 3	✓	✓	✓	✓	✓	✓ 3	✓ 3	✓ 3
✓ 2	1	✓		✓	✓	✓ 4		✓ 3		✓		✓		✓	✓ 3	✓ 3
✓ 2	1	✓	✓	✓	✓	✓ 4	✓ 3	✓	✓	✓	✓	✓	✓	✓	✓ 3	✓ 3
✓ 2	1	✓	✓	✓ 3	✓	✓ 4	✓ 3	✓	✓	✓	✓	✓	✓	✓		✓ 3

Table adapted with permission from the Marijuana Policy Project;⁶⁰ table is not all-encompassing and other medical conditions for use may exist. The reader should refer to individual state laws regarding medicinal cannabis for specific details of approved conditions for use. In addition, states may permit the addition of approved indications; list is subject to change.

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2. Access to marijuana through home cultivation, dispensaries, or some other system that is likely to be implemented;
3. Allows a variety of strains, including more than those labeled as “low THC;” and
4. Allows either smoking or vaporization of some kind of marijuana products, plant material, or extract.

Some of the most common policy questions regarding medical cannabis now include how to regulate its recommendation and indications for use; dispensing, including quality and standardization of cultivars or strains, labeling, packaging, and role of the pharmacist or health care professional in education or administration; and registration of approved patients and providers.

REGULATORY IMPLICATIONS OF MEDICINAL CANNABIS

The regulation of cannabis therapy is complex and unique; possession, cultivation, and distribution of this substance, regardless of purpose, remain illegal at the federal level, while states that permit medicinal cannabis use have established individual laws and restrictions on the sale of cannabis for medical purposes. In a 2013 U.S. Department of Justice memorandum to all U.S. attorneys, Deputy Attorney General James M. Cole noted that despite the enactment of state laws authorizing marijuana production and sale having a regulatory structure that is counter to the usual joint efforts of federal authorities working together with local jurisdictions, prosecution of individuals cultivating and distributing marijuana to seriously ill individuals for medicinal purpose has not been identified as a federal priority.⁶²

There are, however, other regulatory implications to consider based on the federal restriction of cannabis. Physicians cannot legally “prescribe” medicinal cannabis therapy, given its Schedule I classification, but rather in accordance with state laws may certify or recommend patients for treatment. Medical cannabis expenses are not reimbursable through government medical assistance programs or private health insurers. As previously described, the Schedule I listing of cannabis according to federal law and DEA regulations has led to difficulties in access for research purposes; nonpractitioner researchers can register with the DEA more easily to study substances in Schedules II–V compared with Schedule I substances.⁶³ Beyond issues related to procurement of the substance for research purposes, other limitations in cannabis research also exist. For example, the Center for Medicinal Cannabis Research at the University of California–San Diego had access to funding, marijuana at different THC levels, and approval for a number of clinical research trials, and yet failed to recruit an adequate number of patients to conduct five major trials, which were subsequently canceled.⁶⁴ Unforeseen factors, including the prohibition of driving during the clinical trials, deterred patients from trial enrollment. The limited availability of clinical research to support or refute therapeutic claims and indications for use of cannabis for medicinal purposes has frequently left both state legislative authorities and clinicians to rely on anecdotal evidence, which has not been subjected to the same rigors of peer review and scrutiny as well-conducted, randomized trials, to validate the safety and efficacy of medicinal cannabis therapy. Furthermore, although individual single-entity pharmaceutical medications, such as dronabinol, have been isolated, evaluated, and approved for use

by the FDA, a plant cannot be patented and mass produced by a corporate entity.⁶⁵ Despite this limitation, some corporations, including GW Pharmaceuticals, are mass producing cannabis plants and extracting complex mixtures or single cannabinoids for clinical trials.⁶⁵ The complex pharmacology related to the numerous substances and interactions among chemicals in the cannabis plant coupled with environmental variables in cultivation further complicate regulation, standardization, purity, and potency as a botanical drug product.

RELEVANCE TO HOSPITAL PRACTITIONERS

Although the public has largely accepted medicinal cannabis therapy as having a benefit when used under a provider’s supervision, the implications of the use of this substance when patients transition into the acute care setting are additionally complex and multifaceted. The Schedule I designation of cannabis causes hospitals and other care settings that receive federal funding, either through Medicare reimbursement or other federal grants or programs, to pause to consider the potential for loss of these funds should the federal government intercede and take action if patients are permitted to use this therapy on campus. Similarly, licensed practitioners registered to certify patients for state medicinal cannabis programs may have comparable concerns regarding jeopardizing their federal DEA registrations and ability to prescribe other controlled substances as well as jeopardizing Medicare reimbursements. In 2009, U.S. Attorney General Eric Holder recommended that enforcement of federal marijuana laws not be a priority in states that have enacted medicinal cannabis programs and are enforcing the rules and regulations of such a program; despite this, concerns persist.

The argument for or against the use of medicinal cannabis in the acute care setting encompasses both legal and ethical considerations, with the argument against use perhaps seeming obvious on its surface. States adopting medical cannabis laws may advise patients to utilize the therapy only in their own residence and not to transport the substances unless absolutely necessary.⁶⁶ Further, many acute care institutions have policies prohibiting smoking on facility grounds, thus restricting the smoking of cannabis, regardless of purpose or indication. Of note, several Canadian hospitals, including Montreal’s Jewish General Hospital and Quebec’s Centre Hospitalier Universitaire de Sherbrooke, have permitted inpatient cannabis use via vaporization; the pharmacy departments of the respective institutions control and dispense cannabis much like opioids for pain. Canada has adopted national regulations to control and standardize dried cannabis for medical use.^{67,68} There are complicated logistics for self-administration of medicinal cannabis by the patient or caregiver; in particular, many hospitals have policies on self-administration of medicines that permit patients to use their own medications only after identification and labeling by pharmacy personnel. The argument can be made that an herb- or plant-based entity cannot be identified by pharmacy personnel as is commonly done for traditional medicines, although medicinal cannabis dispensed through state programs must be labeled in accordance with state laws. Dispensing and storage concerns, including an evaluation of where and how this product should be stored (e.g., within the pharmacy department and treated as a controlled substance, by security personnel, or with the patient); who should admin-

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ister it, and implications or violations of federal law by those administering treatment; what pharmaceutical preparations should be permitted (e.g., smoked, vaporized, edible); and how it should be charted in the medical record represent other logistical concerns. Inpatient use of medicinal cannabis also carries implications for nursing and medical staff members. The therapy cannot be prescribed, and states may require physicians authorizing patient use to be registered with local programs. In a transition into the acute care setting from the community setting, a different clinician who is not registered could be responsible for the patient's care; that clinician would be restricted in ordering continuation of therapy.

Despite the complexities in the logistics of continuing medicinal cannabis in the acute care setting, proponents of palliative care and continuity of care argue that prohibiting medicinal cannabis use disrupts treatment of chronic and debilitating medical conditions. Patients have been denied this therapy during acute care hospitalizations for reasons stated above.⁶⁹ Permission to use medicinal cannabis in the acute care setting may be dependent on state legislation and restrictions imposed by such laws. Legislation in Minnesota, as one example, has been amended to permit hospitals as facilities that can dispense and control cannabis use; similar legislative actions protecting nurses from criminal, civil, or disciplinary action when administering medical cannabis to qualified patients have been enacted in Connecticut and Maine.^{70–73} Proposed legislation to remove restrictions on the certification of patients to receive medicinal cannabis by doctors at the Department of Veterans Affairs was struck down in June; prohibitions continue on the use of this therapy even in facilities located in states permitting medicinal cannabis use.⁷⁴

CONCLUSION

Despite lingering controversy, use of botanical cannabis for medicinal purposes represents the revival of a plant with historical significance reemerging in present day health care. Legislation governing use of medicinal cannabis continues to evolve rapidly, necessitating that pharmacists and other clinicians keep abreast of new or changing state regulations and institutional implications. Ultimately, as the medicinal cannabis landscape continues to evolve, hospitals, acute care facilities, clinics, hospices, and long-term care centers need to consider the implications, address logistical concerns, and explore the feasibility of permitting patient access to this treatment. Whether national policy—particularly with a new presidential administration—will offer some clarity or further complicate regulation of this treatment remains to be seen.

REFERENCES

1. Drug Enforcement Administration. Office of Diversion Control. Title 21 United States Code (USC) Controlled Substances Act. Subchapter I—Control and enforcement. Part B—Authority to control; standards of controlled substances. §812. Schedules of controlled substances. (b) Placement on schedules; findings required. (1) Schedule I. Springfield, Virginia: U.S. Department of Justice; 1970. [also known as Controlled Substances Act, 21 United States Code § 812(b) (1), 1970]. Available at: www.deadiversion.usdoj.gov/21cfr/21usc/812.htm. Accessed August 5, 2016.
2. World Health Organization. Management of substance abuse: cannabis. 2016. Available at: www.who.int/substance_abuse/facts/cannabis/en. 2016. Accessed November 29, 2016.
3. Substance Abuse and Mental Health Services Administration. Behavioral health trends in the United States: results from the 2014

- national survey on drug use and health. Available at: www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf. Accessed August 5, 2016.
4. Office of National Drug Control Policy. Answers to frequently asked questions about marijuana. Available at: www.whitehouse.gov/ondcp/frequently-asked-questions-and-facts-about-marijuana. Accessed August 5, 2016.
5. Swift A. Support for legal marijuana use up to 60% in U.S. October 19, 2016. Available at: www.gallup.com/poll/196550/support-legal-marijuana.aspx. Accessed November 29, 2016.
6. Quinnipiac University. Allow marijuana for vets with PTSD, U.S. voters say 10-1, Quinnipiac University national poll finds; slim majority say legalize marijuana in general. June 6, 2016. Available at: www.qu.edu/news-and-events/quinnipiac-university-poll/national/release-detail?ReleaseID=2354. Accessed August 5, 2016.
7. Adler JN, Colbert JA. Medicinal use of marijuana—polling results. *N Engl J Med* 2013;368:e30.
8. Kondrad E, Reid A. Colorado family physicians' attitudes toward medicinal marijuana. *J Am Board Fam Med* 2013;26:52–60.
9. Moeller KE, Woods B. Pharmacy students' knowledge and attitudes regarding medical marijuana. *Am J Pharm Educ*. 2015;79:85.
10. National Conference of State Legislatures. State medical marijuana laws. November 9, 2016. Available at: ncsl.org/research/health/state-medical-marijuana-laws.aspx. Accessed November 29, 2016.
11. Food and Drug Administration. FDA and marijuana. July 7, 2016. Available at: www.fda.gov/NewsEvents/PublicHealthFocus/ucm421163.htm. Accessed August 5, 2016.
12. Throckmorton DC. FDA work on medical products containing marijuana. Food and Drug Administration. March 2015. Available at: www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM438966.pdf. Accessed August 5, 2016.
13. Bennett C. Early/ancient history. In: Holland J, ed. *The Pot Book: A Complete Guide to Cannabis*. Rochester, Vermont: Park Street Press; 2010.
14. Zias J, Stark H, Sellman J, et al. Early medical use of cannabis. *Nature* 1993;363:215.
15. Malmo-Levine D. Recent history. In: Holland J, ed. *The Pot Book: A Complete Guide to Cannabis*. Rochester, Vermont: Park Street Press; 2010.
16. Musto DF. The Marijuana Tax Act of 1937. *Arch Gen Psychiatry* 1972;26:101–108.
17. Giancaspro GI, Kim N-C, Venema J, et al. The advisability and feasibility of developing USP standards for medical cannabis. U.S. Pharmacopeial Convention. Available at: www.usp.org/sites/default/files/usp_pdf/EN/USPNF/usp-nf-notices/usp_stim_article_medical_cannabis.pdf. Accessed August 5, 2016.
18. Cameron JM, Dillinger RJ. Narcotic Control Act. In: Kleiman MAR, Hawdon JE, eds. *Encyclopedia of Drug Policy*. Thousand Oaks, California: SAGE Publications, Inc.; 2011:543–545.
19. State marijuana laws in 2016 map. *Governing*. November 11, 2016. Available at: www.governing.com/gov-data/state-marijuana-laws-map-medical-recreational.html. Accessed November 29, 2016.
20. Sidney S. Comparing cannabis with tobacco—again. *BMJ*. 2003;327:635–636.
21. Norml. About marijuana. Available at: <http://norml.org/about-marijuana>. Accessed August 9, 2016.
22. Clark PA, Capuzzi K, Fick C. Medical marijuana: medical necessity versus political agenda. *Med Sci Monit* 2011;17:RA249–RA261.
23. National Institute on Drug Abuse. Drug facts: is marijuana a medicine? July 2015. Available at: www.drugabuse.gov/publications/drugfacts/marijuana-medicine. Accessed February 11, 2016.
24. Should marijuana be a medical option? ProCon.org. December 28, 2016. Available at: <http://medicalmarijuana.procon.org>. Accessed February 11, 2016.
25. MacDonald K, Pappas K. Why not pot? *Innov Clin Neurosci* 2016;13:13–22.
26. McPartland JM, Duncan M, Di Marzo V, et al. Are cannabidiol and Δ9-tetrahydrocannabinol negative modulators of the endocannabinoid system? A systematic review. *Br J Pharmacol*. 2014;172:737–753.
27. Kaur R, Ambwani SR, Singh S. Endocannabinoid system: A multifaceted therapeutic target. *Curr Clin Pharmacol* 2016;11:110–117.

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28. McPartland JM, Guy GW, Di Marzo V. Care and feeding of the endocannabinoid system: a systematic review of potential clinical interventions that upregulate the endocannabinoid system. *PLoS One*. 2014;9:e89566. doi: 10.1371/journal.pone.0089566.
29. Ben-Shabat S, Fride E, Sheskin T, et al. An entourage effect: inactive endogenous fatty acid glycerol esters enhance 2-arachidonoyl-glycerol cannabinoid activity. *Eur J Pharmacol* 1998;353:23–31.
30. Izzo AA, Borrelli F, Capasso R, et al. Nonpsychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends Pharmacol Sci* 2009;30:515–527.
31. Pertwee RG, Howlett AC, Abood ME, et al. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB₁ and CB₂. *Pharmacol Rev* 2010;62:588–631.
32. Fasinu PS, Phillips S, ElSohly MA, Walker LA. Current status and prospects for cannabidiol preparations as new therapeutic agents. *Pharmacotherapy* 2016;36:781–796.
33. Zhornitsky S, Potvin S. Cannabidiol in humans—the quest for therapeutic targets. *Pharmaceuticals (Basel)* 2012;5:529–552. doi:10.3390/ph5050529.
34. Borodovsky JT, Crosier BS, Lee DC, et al. Smoking, vaping, eating: Is legalization impacting the way people use cannabis? *Int J Drug Policy* 2016;36:141–147.
35. Huestis MA. Pharmacokinetics and metabolism of the plant cannabinoids, delta-9-tetrahydrocannabinol, cannabidiol, and cannabiol. *Handb Exp Pharmacol* 2005;168:657–690.
36. Huestis MA, Henningfield JE, Cone EJ. Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. *J Anal Toxicol* 1992;16:276–282.
37. Hartman RL, Brown TL, Milavetz G, et al. Controlled cannabis vaporizer administration: blood and plasma cannabinoids with and without alcohol. *Clin Chem* 2015;61:850–869.
38. Ohlsson A, Lindgren JE, Wahlen A, et al. Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clin Pharmacol Ther* 1980;28:409–416.
39. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 2003;42:327–360.
40. Stout SM, Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. *Drug Metab Rev* 2014;46:86–95.
41. Sativex oral mucosal spray. electronic Medicines Compendium (eMC). May 2015. Available at: www.medicines.org.uk/emc/medicine/23262. Accessed August 9, 2016.
42. Marinol (dronabinol capsules USP) prescribing information. North Chicago, Illinois: AbbVie; 2016.
43. Volkow ND, Baler RD, Compton WM, et al. Adverse health effects of marijuana use. *N Engl J Med* 2014;370:2219–2227.
44. Gage SH, Hickman M, Zammit S. Association between cannabis and psychosis: epidemiologic evidence. *Biol Psychiatry* 2016;79:549–556.
45. Curran HV, Freeman TP, Mokrysz C, et al. Keep off the grass? Cannabis, cognition, and addiction. *Nat Rev Neurosci* 2016;17:293–306.
46. Joshi M, Joshi A, Bartter T. Marijuana and lung diseases. *Curr Opin Pulm Med* 2014;20:173–179.
47. Blanco C, Hasin DS, Wall MM, et al. Cannabis use and risk of psychiatric disorders: prospective evidence from a U.S. national longitudinal study. *JAMA Psychiatry* 2016;73:388–395.
48. de Graaf R, Radovanovic M, van Laar M, et al. Early cannabis use and estimated risk of later onset of depression spells: Epidemiologic evidence from the population-based World Health Organization World Mental Health Survey Initiative. *Am J Epidemiol* 2010;172:149–159.
49. Hackam DG. Cannabis and stroke: systematic appraisal of case reports. *Stroke* 2015;46:852–856.
50. Barber PA, Pridmore HM, Krishnamurthy V, et al. Cannabis, ischemic stroke, and transient ischemic attack: a case-control study. *Stroke* 2013;44:2327–2329.
51. Barber PA, Roberts S, Spriggs DA, et al. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana: what cardiologists need to know. *Am J Cardiol* 2014;113:1086.
52. Karila L, Roux P, Rolland B, et al. Acute and long-term effects of cannabis use: a review. *Curr Pharm Des* 2014;20:4112–4118.
53. Turcotte D, Le Dorze JA, Esfahani F, et al. Examining the roles of cannabinoids in pain and other therapeutic indications: a review. *Expert Opin Pharmacother* 2010;11:17–31.
54. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. *CMAJ* 2008;178:1669–1678.
55. Lynch ME, Campbell F. Cannabinoids for treatment of chronic noncancer pain: a systematic review of randomized trials. *Br J Clin Pharmacol* 2011;72:735–744.
56. Smith LA, Azariah F, Lavender VTC, et al. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. *Cochrane Database Syst Rev* 2015 Nov 12;(11):CD009464.
57. Gloss D, Vickrey B. Cannabinoids for epilepsy. *Cochrane Database Syst Rev* 2014 Mar 5;(3):CD009270.
58. American Academy of Neurology. Efficacy and safety of the therapeutic use of medical marijuana (cannabis) in selected neurologic disorders. Available at: www.aan.com/Guidelines/home/Get-GuidelineContent/651. Accessed August 16, 2016.
59. van den Elsen GA, Ahmed AI, Lammers M, et al. Efficacy and safety of medical cannabinoids in older subjects: a systematic review. *Ageing Res Rev* 2014;14:56–64.
60. Marijuana Policy Project. State-by-state medical marijuana laws 2015. Available at: [www.mpp.org/issues/medical-marijuana/state-by-state-medical-marijuana-laws-report](http://www.mpp.org/issues/medical-marijuana/state-by-state-medical-marijuana-laws/state-by-state-medical-marijuana-laws-report). Accessed August 10, 2016.
61. 25 legal medical marijuana states and DC: laws, fees, and possession limits. Available at: http://medicalmarijuana.procon.org/view_resource.php?resourceID=000881#DC. Accessed August 10, 2016.
62. Cole JM. Guidance regarding marijuana enforcement. August 29, 2013. Available at: www.justice.gov/iso/opa/resources/3052013829132756857467.pdf. Accessed August 8, 2016.
63. DEA Diversion Control Division. DEA Form 225—New application for registration. Available at: www.deadiversion.usdoj.gov/drugreg/reg_apps/225/225_instruct.htm. Accessed August 10, 2016.
64. Center for Medicinal Cannabis Research. University of California, San Diego. Available at: <http://cmcr.ucsd.edu>. Accessed December 4, 2016.
65. Cannabinoid Research Institute. GW Pharmaceuticals. Available at: www.gwpharm.com/products-pipeline/research-trials/cannabinoid-research-institute. Accessed December 4, 2016.
66. New Jersey Department of Health. Guidelines for patients and caregivers. Available at: www.state.nj.us/health/medicalmarijuana/patients/guidelines. Accessed August 10, 2016.
67. Dyer O. Quebec hospitals allow inpatient use of weed. *CMAJ* 2014;186:E438.
68. Health Canada. Medical use of marihuana. July 8, 2016. Available at: www.hc-sc.gc.ca/dhp-mps/marihuana/index-eng.php. Accessed August 9, 2016.
69. Graham G. Sanford hospital patient denied medical marijuana. *Portland Press Herald*. August 23, 2015. Available at: www.pressherald.com/2015/08/23/hospital-patient-denied-medical-marijuana-lotion. Accessed August 8, 2016.
70. Nelson T. Minnesota hospitals will be able to dispense medical marijuana. May 28, 2015. *Minnesota Public Radio News*. Available at: www.mprnews.org/story/2015/05/28/medical-marijuana-minnesota-hospitals. Accessed August 8, 2016.
71. Revisor of Statutes, State of Minnesota. Chapter 74—H.F.No.1792. May 22, 2015. Available at: www.revisor.mn.gov/laws/?year=2015&type=0&doctype=Chapter&id=74&format=pdf. Accessed August 8, 2016.
72. State of Connecticut. Raised Bill No. 5450—An act concerning the palliative use of marijuana. Effective October 1, 2016. Available at: www.cga.ct.gov/2016/TOB/h/2016HB-05450-R00-HB.htm. Accessed August 8, 2016.
73. State of Maine. Chapter 475—Public Law: An act to increase patient safety in Maine’s medical marijuana program. Passed April 15, 2016. Available at: www.mainelegislature.org/legis/bills/getPDF.asp?paper=SP0256&item=3&num=127. Accessed August 8, 2016.
74. Tritten TJ. VA medical pot gets booted from budget bill. *Stars and Stripes*. June 24, 2016. Available at: www.stripes.com/news/va-medical-pot-gets-booted-from-budget-bill-1.416170. Accessed August 10, 2016. ■

Review Article

Marijuana Compounds: A Nonconventional Approach to Parkinson's Disease Therapy

Mariana Babayeva, Haregewein Assefa, Paramita Basu, Sanjeda Chumki, and Zvi Loewy

Touro College of Pharmacy, 230 West 125th Street, Room 530, New York, NY 10027, USA

Correspondence should be addressed to Mariana Babayeva; mariana.babayeva@touro.edu

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Parkinson's disease (PD), a neurodegenerative disorder, is the second most common neurological illness in United States. Neurologically, it is characterized by the selective degeneration of a unique population of cells, the nigrostriatal dopamine neurons. The current treatment is symptomatic and mainly involves replacement of dopamine deficiency. This therapy improves only motor symptoms of Parkinson's disease and is associated with a number of adverse effects including dyskinesia. Therefore, there is unmet need for more comprehensive approach in the management of PD. Cannabis and related compounds have created significant research interest as a promising therapy in neurodegenerative and movement disorders. In this review we examine the potential benefits of medical marijuana and related compounds in the treatment of both motor and nonmotor symptoms as well as in slowing the progression of the disease. The potential for cannabis to enhance the quality of life of Parkinson's patients is explored.

1. Introduction

Marijuana, the crude product (dried flowers, stems, seeds, and leaves) derived from the cannabis sativa plant, consists of more than 85 phytocannabinoids [1, 2]. The term phytocannabinoids is used to differentiate these plant-derived cannabinoids from the synthetic cannabinoids and the structurally different endogenous cannabinoids (endocannabinoids). Among the phytocannabinoids, Cannabidiol (CBD) and Δ^9 -Tetrahydrocannabinol (Δ^9 -THC, THC) are the major constituents of marijuana [3]. Δ^9 -THC is a psychoactive agent with analgesic and muscle relaxant property [3, 4]. While CBD is a nonpsychoactive compound and has been shown to have hypnotic, anxiolytic, antipsychotic, antioxidant, and neuroprotective effects [5], THC is a partial agonist at the cannabinoid receptor 1 (CB1) and receptor 2 (CB2). Unlike Δ^9 -THC, CBD has antagonistic/inverse agonistic property at CB1 receptor and appears to modulate Δ^9 -THC-associated side effects including anxiety, tachycardia, and hunger [3]. CBD also appears to potentiate the effect of endocannabinoids by inhibiting their inactivation, thereby alleviating psychotic symptom [6].

Despite the placement of marijuana in the schedule 1 category under the US Federal Controlled Substance Act [7] and the US Federal Government's continued opposition on its legalization, 24 states and Washington DC have enacted laws allowing marijuana to treat certain medical conditions [8]. The range and types of disease conditions for which medical marijuana have been approved vary from state to state. The most common disease conditions approved by the states include cancer, HIV/AIDS, glaucoma, chronic and/or severe pain, seizure/epilepsy, cachexia, and multiple sclerosis. Moreover, two cannabinoids (dronabinol and nabilone) have been approved by the FDA for clinical use. The synthetically produced Δ^9 -THC, dronabinol (Marinol®), is a schedule III drug, which is indicated in the treatment of chemotherapy-induced nausea and emesis as well as anorexia associated with weight loss in AIDS patients. A synthetic cannabinoid, nabilone (Cesamet®), is a schedule II drug that is indicated for the treatment of nausea and vomiting associated with cancer chemotherapy. Another cannabinoid, Cannabidiol (Epidiolex®), is in a clinical trial for the treatment of drug-resistant epilepsy in children [9]. A phytocannabinoid preparation, nabiximols (Sativex®), has been approved for the

treatment of spasticity due to multiple sclerosis in a number of countries outside the United States. Nabiximols is an extract of *Cannabis sativa* L that consists of mainly THC and CBD [10, 11].

Although recent studies have provided strong evidence for the therapeutic benefit of medical marijuana [12–16], increasing access to cannabis and/or cannabinoids can result in side effects such as addiction, respiratory illness, and decline in cognitive processing. Cannabis use has been indicated as a potential cause, aggravator, or masker of major psychiatric symptoms, including psychotic, depressive, and anxiety disorders, particularly in young people [17–19]. Other negative effects include working memory deficits, reduced attention and processing speed, anhedonia, abnormal social behavior, and susceptibility to mood and anxiety disorders [20, 21]. While adult users seem comparatively resistant to cannabis-induced behavioral and brain morphologic changes, the individuals who start using cannabis during their early teens can have more severe and more long-lasting effects [22].

The target of medical marijuana and its constituents is the endocannabinoid system, which is involved in the modulation of a number of physiological functions. The endocannabinoid system includes the endocannabinoids, the cannabinoid receptors, and the enzymes involved in the biosynthesis and inactivation of the endocannabinoids [23]. The cannabinoid receptors are mainly expressed in the central nervous system and the immune system, but they have also been identified in a number of other parts of the body including the cardiovascular system, the peripheral nervous system, the reproductive system, and the gastrointestinal tract. Due to its wide distribution and effects on a range of biological process, the cannabinoid system has become an attractive target for the development of drugs that can potentially be used for the treatment of a number of pathological conditions including mood disorders and movement disorders such as PD [24]. Components of the endocannabinoid system are abundant in the striatum and other parts of the basal ganglia and play a crucial role in modulating dopamine activity and motor functions [25–27].

Parkinson's disease (PD) is the second most common neurodegenerative disorder following Alzheimer's disease and the 14th leading cause of death in all age groups in the United States [28]. The prevalence of PD increases with age and is shown to be higher in males than females in some age groups [29]. The number of people with PD is projected at approximately 9 million by 2030 in the 15 most populous countries in the world [30, 31]. Neurologically PD is characterized by the destruction of dopaminergic cells in the pars compacta region of the substantia nigra in the midbrain, resulting in dopamine deficiency in the nerve terminals of the striatum in the forebrain [32]. These changes cause impairments not just to the motor system but also to the cognitive and neuropsychological systems [33]. The nigrostriatal pathway is one of the dopamine pathways in the brain that regulates movement. The exact cause for the loss of neuronal cells is unknown, and the trigger of dopaminergic degeneration seems to be multifactorial including environmental factors and genetic susceptibilities

[34–36]. Clinically, PD is characterized by resting tremor, muscle rigidity, bradykinesia, and postural instability [32, 34, 37, 38] and it is also associated with a number of nonmotor symptoms including depression, anxiety, constipation, orthostatic hypotension, fatigue, and sleep disorders, as well as, in advanced disease, dementia [39–44]. Although dopamine deficiency accounts for the major motor symptoms of the disease, loss of noradrenergic and serotonergic nerve terminals in the limbic system may account for several of the nonmotor features seen in Parkinson's disease [45, 46].

Current therapy involves treatment of motor symptoms of PD through replacement of dopamine deficiency [47]. This includes (1) enhancement of the synthesis of brain dopamine by administration of levodopa, a dopamine precursor, (2) direct stimulation of dopamine receptors, (3) decreasing dopamine catabolism, and (4) stimulation of dopamine release and inhibition of dopamine reuptake from presynaptic sites. Another therapy involves restoring the normal balance of cholinergic and dopaminergic actions on the basal ganglia using anticholinergic drugs [47–49].

However these drugs treat only motor symptoms of Parkinson's disease and are associated with a number of adverse effects. Long-term use of levodopa, the mainstay therapy for PD, is associated with motor fluctuations [50] and levodopa-induced dyskinesia [51–53]. The monoamine oxidase B (MAO-B) inhibitors (selegiline and rasagiline) as well as inhibitors of catechol-o-methyltransferase, COMT (tolcapone and entacapone), are used mostly to reduce the motor fluctuations associated with levodopa therapy due to their levodopa-sparing effect [54–59]. Several dopamine agonists including pramipexole, ropinirole, rotigotine, and apomorphine are used as monotherapy in early stage of Parkinson disease or as adjunctive therapy with levodopa in patients with advanced PD in order to reduce motor fluctuations [56, 60–64]. In addition to their limited efficacy on motor symptoms and their adverse effects, drugs that are currently used for the treatment of PD do not have an effect on disease progression. Therefore, there is an urgent need for the development of safer drugs that treat both the motor and nonmotor symptoms of PD as well as drugs that slow the progression of the disease.

Medical marijuana has been demonstrated to improve motor symptoms including tremor, rigidity, and bradykinesia as well as nonmotor symptoms such as pain and sleep disorders of PD in observational studies [65]. Survey of PD patients in Colorado, USA, also indicated the beneficial effects of marijuana in alleviating nonmotor symptoms of PD [66]. Cannabidiol (CBD), one of the major constituents of marijuana, has been shown to be effective in the treatment of psychosis and sleep disorders in PD patients [67–69]. Another phytocannabinoid, Δ^9 -tetrahydrocannabinol (Δ^9 -THCV, THCV), was studied in animal disease model of PD and found to have neuroprotective and symptom-relieving effects [70]. Therefore, marijuana may provide an alternative or add-on therapy for Parkinson's disease. In addition, Parkinson's disease has been listed as one of the disease conditions for which medical marijuana is allowed in Connecticut, Illinois, Massachusetts, New Hampshire, New

Mexico, and New York. However, it may also be covered under chronic illnesses in several other states.

In this review we seek to investigate any scientific evidence that indicates the potential use of marijuana and/or its components for the treatment of Parkinson's disease. The review aims to (i) examine briefly current treatment and the unmet need of PD therapy, (ii) assess the role of the cannabinoid system in the modulation of movement and neuroprotection, (iii) look at the mechanism of action of marijuana constituents in the modulation of movement and PD-associated disorders, (iv) assess other beneficial effects of marijuana that contribute to the amelioration of PD, and (v) gather scientific evidence on the clinical benefit of marijuana and/or its constituents in PD patients.

2. Marijuana and Its Influence on the Endocannabinoid System

Cannabis has been used to treat disease since ancient times. Marijuana is derived from the *Cannabis sativa L.* plant. Marijuana contains the active chemicals known as cannabinoids. At least 85 cannabinoids have been identified as unique compounds in *Cannabis* [1]. The therapeutic potential of many of these ligands still remains largely unexplored prompting a need for further research. The chemicals responsible for the medicinal effects of marijuana are D9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD) [71, 72]. THC is the major psychoactive ingredient, acting primarily upon the central nervous system where it affects brain function. CBD is the major nonpsychoactive ingredient in cannabis and produces neuroprotective and anti-inflammatory effects [73]. Both compounds, TCH and CBD, have anticonvulsant properties [74]. Cannabinoids have also potential to alleviate motor disorders by reducing motor impairments and neuron degeneration [75]. In addition, cannabinoids have been shown to be effective in preclinical studies involving excitotoxicity, oxidative stress, neuroinflammation, and motor complications associated with PD [76].

Some cannabinoids (endocannabinoids or ECBs) are found in the body. Initially, ECBs were discovered in the brain and subsequently in the periphery in humans and animals. Endocannabinoids are produced by cultured neurons [77], microglia, and astrocytes [78]. ECBs interact with the endocannabinoid system and aid in regulation of memory, pleasure, concentration, thinking, movement and coordination, sensory and time perception, appetite, and pain [24, 79, 80]. The ECBs activate two guanine nucleotide-binding protein-(G-protein-) coupled cell membrane receptors, consequently named the cannabinoid type 1 (CB1) and type 2 (CB2) receptors [81]. CB1 receptors are located primarily in the central and peripheral neurons and CB2 receptors are predominantly found in immune cells [82]. CB1 receptors are important mediators in signaling pathways and have been identified on both glutamatergic and gamma-aminobutyric (GABA) neurons [83]. It is believed that one important role of the neuronal CB1 component is to modulate neurotransmitter release in a manner that maintains homeostasis by preventing the development of excessive neuronal activity in the central

nervous system [82]. Animal models illustrate that activation of the CB1 receptor by their endogenous ligands can result in prominent neuroprotective effects and may prevent epileptic seizures [84]. Other studies suggest that activation of CB1 receptors offers neuroprotection against dopaminergic lesion and the development of L-DOPA-induced dyskinesias [85]. CB2 receptors are closely related to CB1 and are mainly expressed on T cells of the immune system, on macrophages and B cells, and in hematopoietic cells [86]. They are also expressed on peripheral nerve terminals where these receptors play a role in antinociception and the relief of pain [87]. In the brain, CB2 receptors are mainly expressed by microglial cells, where their role remains unclear [88].

The major identified ECBs are arachidonoyl ethanolamide (anandamide, AEA), 2-arachidonoyl glycerol (2-AG), O-arachidonoyl ethanolamine (virodhamine), and 2-arachidonoyl glyceryl ether (noladin ether) [89]. Both AEA and 2-AG are specific ligands of CB1 and CB2 receptors. Besides having activity on CB1 and CB2 receptors, AEA also has full agonistic activity at TRPV1 receptor [90]. AEA is localized in the brain and periphery [91]. In the brain AEA shows high distribution in the hippocampus, thalamus, striatum, and brainstem and to a lesser extent in the cerebral cortex and cerebellum [92]. Lower concentrations of AEA are found in human serum, plasma, and cerebrospinal fluid [93]. Similarly, 2-AG is observed in both the brain and periphery, although its concentration is almost 150 times higher in brain compared to that of AEA [92, 94, 95]. 2-AG has greater potency, stability, and agonistic activity at CB1 and CB2 receptors compared to that of AEA [96, 97]. Two prominent areas involved in the control of movement, such as the globus pallidus and the substantia nigra, contain not only the highest densities of CB1 receptors [88], but also the highest levels of ECBs, especially AEA [98, 99]. Tissue levels of AEA are regulated by fatty acid amide hydrolase (FAAH) [100]. It has also been shown that the basal ganglia contain the precursor of AEA [98, 99], supporting the theory of in situ synthesis for this compound. Studies have demonstrated that AEA synthesis is regulated by dopaminergic D2 receptors in the striatum, suggesting that the endocannabinoid system acts as an inhibitory feedback mechanism countering the dopamine-induced facilitation of motor activity [101].

Marijuana compound THC is CB₁ and CB₂ receptor partial agonist [82]. Due to the structural similarity of natural cannabinoid THC to the endogenous cannabinoid AEA, many therapeutic advantages of THC have been identified, such as lowering ocular pressure, inhibiting smooth muscle contractions, and increasing appetite [102]. When smoked, THC is rapidly absorbed from the lungs into the bloodstream and has an effect on the cannabinoid receptors. The central nervous system and specific areas of the brain contain the highest concentration of cannabinoid receptors. Therefore, cannabis or THC administration can create an overexcitation of the system that results in altered perceptions, pleasure, and mood [103].

Unlike THC, CBD has little affinity for CB1 and CB2 receptors but acts as an indirect antagonist of cannabinoid agonists. While this should cause CBD to reduce the effects of THC, it may potentiate THC's effects by increasing CB1

receptor density or through another CBI-related mechanism [73]. CBD is also an inverse agonist of CB2 receptors. CBD can counteract some of the functional consequences of CBI activation in the brain, possibly by indirect enhancement of adenosine A1 receptors activity through equilibrative nucleoside transporter (ENT) inhibition [73]. CBD helps to augment some of THC's beneficial effects, as it reduces the psychoactivity of THC, enhances its tolerability, and widens THC's therapeutic window [104].

Other cannabinoids can also contribute to the cannabis medicinal effects. Studies in experimental models and humans have suggested anti-inflammatory, neuroprotective, anxiolytic, and antipsychotic properties of chemicals extracted from marijuana [6, 15, 82, 105, 106].

3. Cannabinoids and Parkinson's Disease

3.1. Changes in the Cannabinoid System in Parkinson's Disease. Recent data from several studies indicate the important role of the endocannabinoid system in Parkinson's disease. The components of the endocannabinoid system are highly expressed in the neural circuit of basal ganglia, which is part of a complex neuronal system. This neuronal system coordinates activities from different cortical regions that directly or indirectly participate in the control of movement [107, 108]. In the basal ganglia, the endocannabinoid system bidirectionally interacts with dopaminergic, glutamatergic, and GABAergic signaling systems [109]. Endocannabinoids play a dominant role in controlling transmission at synapses between cortical and striatal neurons, in mediating the induction of a particular form of synaptic plasticity, and in modulating basal ganglia activity and motor functions [110]. The progressive loss of dopaminergic neurons that occurs in PD leads to lower striatal levels of dopamine. These low levels of dopamine result in the alteration of the equilibrium between the direct and the indirect basal ganglia pathways and ECB signaling [111].

The cannabinoid signaling system mentioned above experiences a biphasic pattern of changes during the progression of PD [112]. Early and presymptomatic PD stages, characterized by neuronal malfunction with little evidence of neuronal death, are associated with desensitization/down-regulation of CBI receptors and aggravation of various cytotoxic insults such as excitotoxicity, oxidative stress, and glial activation [113]. However, intermediate and advanced stages of PD, characterized by a deep nigral degeneration and manifestation of major Parkinsonian symptoms, are associated with upregulatory responses of CBI receptors and the endocannabinoid ligands [113]. This could explain the potential of CBI receptor ligands in alleviating common PD symptoms.

In the brain, CBI receptors are expressed by GABAergic neurons innervating the external and internal segments of the globus pallidus and the substantia nigra [114–116]. CBI receptors are also present in the corticostriatal glutamatergic terminals and in the excitatory projections from the subthalamic nucleus to the internal segment of the globus pallidus and the substantia nigra [114–116]. Within the striatum, CBI receptors

are expressed in parvalbumin immune-reactive interneurons, cholinergic interneurons, and nitric oxide synthase-positive neurons [117, 118]. Animal models of Parkinson's disease show an increase in the density of CBI receptors, levels of endogenous ligands, and CBI receptor binding in the basal ganglia [119–122]. Endogenous cannabinoids activate CBI receptors on presynaptic axons and reduce neurotransmitter and glutamate release, working as retrograde synaptic messengers released from postsynaptic neurons [123]. Similarly, activation of CBI receptors inhibits both glutamate release from substantia nigra afferents and GABA release from striatal afferents. At the same time, activation of presynaptic CBI receptors in the external segments of the globus pallidus can increase local GABA levels by reducing GABA reuptake from striatal afferents to the nucleus and decrease GABA release from striatal afferents of the substantia nigra [114, 116, 118]. Based on these evidences, it is thought that the function of the basal ganglia neuronal system is controlled by ECB. The presence of endocannabinoid systems in different neural structures and their interaction with dopaminergic, glutamatergic, and GABAergic neurotransmitter signaling systems make the components of endocannabinoid system ideal targets for a novel nondopaminergic treatment of PD.

Endocannabinoid signaling is also bidirectionally linked to dopaminergic signaling within the basal ganglia [118]. The CBI, D1, and D2 dopamine receptors are localized in the striatum [114, 115]. In animal models, CBI and D2 dopamine receptors share a common pool of G proteins, suggesting the link of their signal transduction mechanisms [124, 125]. In addition, D2 receptor stimulation resulted in release of ECBs in the striatum [101]. However, stimulation of CBI receptors completely inhibited D1-dopamine receptor mediated activation of adenylyl cyclase and decreased GABA release from striatal afferents of dopaminergic neurons of the substantia nigra resulting in an increased firing of these cells [114–116].

Another receptor involved in control of movement is transient receptor potential vanilloid type 1 (TRPV1), which is expressed in sensory neurons and basal ganglia circuitry of dopaminergic neurons [126, 127]. TRPV1 receptors are molecular integrators of nociceptive stimuli activated by endovanilloids [128]. TRPV1 also interacts with ECB. In particular, anandamide is one of the major endogenous activators of TRPV1 [129–131]. Studies have revealed that motor behavior can be suppressed by the activation of vanilloid receptors [98, 99], suggesting that TRPV1 receptors might play a role in the control of motor function.

3.2. Preclinical Data on the Endocannabinoid System as a Target for Parkinson's Disease Therapy. The association of cannabinoids with regulation of motor functions is well established [132–135]. The effect of the cannabinoids on motor activity depends on the impact of the endocannabinoid system on the dopaminergic, glutamatergic, and GABAergic signaling systems throughout the basal ganglia [112, 136]. The high density of cannabinoid, dopamine, and vanilloid-like receptors coupled with ECBs within the basal ganglia and cerebellum suggests a potential therapeutic role for the

cannabinoids in the control of voluntary movement and in movement disorders such as Parkinson's disease [98, 99, 121, 137]. Additional indications of an important role of the endocannabinoid system in the control of movement involve an inhibitory action of cannabinoids through fine tuning of various classical neurotransmitters activity [138], prominent changes in transmission of ECBs in the basal ganglia [139], and alteration of the CB1 binding as well as CB1 availability in the substantia nigra [85, 112, 119, 120, 140, 141]. These data support the idea that cannabinoid- based compounds act on vital pathways of endocannabinoid transmission and therefore might be of therapeutic interest due to their potential to diminish motor symptoms in extrapyramidal disorders such as Parkinson's disease [27, 76, 142].

Research with cannabinoid agonists and antagonists demonstrates that the cannabinoids can modulate motor activity and produce alterations in corresponding molecular correlates [129, 143–145]. It has been widely reported that synthetic, plant-derived, or endogenous cannabinoid agonists exert a powerful motor inhibition in laboratory species [129, 144, 146–149]. This hypokinetic effect was shown to be mediated by the activation of CB1 receptors in neurons of the basal ganglia circuitry [88, 137, 141, 150–152]. Stimulation of the CB1 receptor by a synthetic cannabinoid HU-210 decreased spontaneous glutamatergic activity and reduced the rotations induced by levodopa/carbidopa by 34% in PD rats [153, 154]. Administration of CB1 receptor agonists THC and two synthetic cannabinoids WIN 55,212-2 and CP 55,940 increased extracellular dopamine concentrations in rats [152, 155, 156]. WIN 55,212-2 and CP 55,940 also weakened contralateral rotations induced by a selective D₁/D₅ receptor partial agonist SKF38393 without developing catalepsy in PD rats [148]. In a gender study THC produced an increase in tyrosine hydroxylase activity in parkin-null male mice (a model of early stages of PD) and caused a motor inhibition that was significantly greater compared to wild-type animals [122]. Treatment with THC inhibited motor activity and produced catalepsy in rats [109, 144, 146, 147] and caused antinociception and ring immobility in mice [157]. In other studies THC diminished the motor inhibition caused by 6-hydroxydopamine [70] and potentiated the hypokinetic effect of reserpine in rats more than 20-fold [135]. However, in a primate model of Parkinson's disease THC did not affect locomotor activity but increased bradykinesia [125].

Administration of WIN 55,212-2 increased stimulation of GTPγ_s binding in the caudate nucleus, putamen, globus pallidus, and substantia nigra of marmosets, indicating an effective activation of CB1 signaling mechanisms [119, 120]. WIN 55,212-2 produced a dose-dependent reduction of the spontaneous motor activity and catalepsy in mutant Syrian hamsters, increased antidystonic efficacy of benzodiazepines [158], and significantly reduced the antikinetic effects of quinpirole in the reserpine-treated rats [159]. Treatment with WIN 55,212-2 also reduced levodopa-induced dyskinesias, attenuated axial, limb, and severe orolingual abnormal involuntary movements in 6-hydroxydopamine- (6-OHDA-) lesioned rats [160–163]. An endogenous cannabinoid agonist oleylethanolamide (OAE) produced reduction in dyskinetic contralateral rotations correlated with reduction of molecular

associates of L-DOPA-induced dyskinesia: reduced FosB striatal overexpression and phosphoacetylation of histone 3 [164]. Another synthetic agonist levonantradol decreased general and locomotor activity and increased bradykinesia in a primate model of Parkinson's disease [125]. Nabilone, a synthetic cannabinoid agonist, coadministered with levodopa significantly decreased total dyskinesia compared with levodopa alone treatment and increased the duration of antiparkinsonian action of levodopa by 76% in PD marmosets [165, 166].

Cannabinoid agonist anandamide (AEA) and its synthetic analog methanandamide increased the extracellular dopamine levels in the nucleus accumbens shell of rats by the activation of the mesolimbic dopaminergic system [167]. This dopamine increase was inhibited by the cannabinoid CB1 receptor antagonist rimonabant [167]. However, recent discoveries indicate that AEA is also able to activate vanilloid VR(1) receptors and that the activation of these receptors might also be responsible for changes in nigrostriatal dopaminergic activity and anandamide-induced hypokinesia [168–170]. AEA produced a tonic facilitation of glutamate release in the substantia nigra via stimulation of VRI receptors, indicating the involvement of this receptor in motor and cognitive functions of the dopaminergic system [171]. Preclinical data have shown that AEA decreased the activity of nigrostriatal dopaminergic neurons and produced hypokinesia that was completely reversed by an antagonist of vanilloid-like receptors, capsazepine [129]. Additional studies have demonstrated that AEA inhibited ambulation and stereotypic behavior, increased inactivity, and occluded the effects of an agonist of vanilloid VR₁ receptors, livanil, on locomotion in mice, suggesting a common mechanism of action for the two compounds [170]. Treatment with anandamide lowered motor activity with the maximal inhibition by approximately 85% and produced hypothermia and analgesia in mice, increased the inactivity time, and markedly decreased the ambulation and the frequency of spontaneous non-ambulatory activities in rats [146, 147, 172, 173]. Moreover, AEA produced a decrease in spontaneous motor activity in laboratory animals similar to the reported actions of THC [129, 145, 153, 170]. The hypokinetic actions of AEA were boosted by coadministration with a selective inhibitor of endocannabinoid uptake N-(3-furylmethyl) eicosa-5,8,11,14-tetraenamide, UCM707 [174].

Tissue concentrations of endocannabinoids are important for producing motor effects. Levels and activities of AEA and 2-AG can be manipulated by inhibition of FAAH enzyme, the action of which is reduced in experimental models of PD [153, 175]. Animal studies have shown that the FAAH enzyme inhibitor [3-(3-carbamoylphenyl) phenyl] N-cyclohexylcarbamate (URB597) magnified and prolonged a rapid, brief dopamine increase that was produced by AEA [167]. Additional studies have confirmed that FAAH inhibition remarkably increases AEA tissue levels but reduces 2-AG levels [176, 177]. To determine whether FAAH inhibition has beneficial impact on PD symptoms the effect of the FAAH inhibitor, URB597, was studied in MPTP- lesioned marmosets. Treatment with URB597 increased plasma levels

of AEA, did not modify the antiparkinsonian actions of L-DOPA, and reduced the magnitude of hyperactivity to levels equivalent to those seen in normal animals [178]. In PD mice URB597 prevented induced motor impairment [179]. Moreover, other FAAH inhibitors, JNJ1661010 and TCF2, also have anticataleptic properties [179]. These results reveal that FAAH inhibition may represent a new strategy for treatment of PD.

Overall, these results indicate that endogenous or exogenous cannabinoid agonists activate the dopaminergic system and play a very important role in modulation of motor behavior [180]. In addition to the effects on movement activity, cannabinoid agonists have demonstrated neuroprotective properties, suggesting that the cannabinoids have a promising pharmacological profile for not only improving Parkinsonian symptoms but also delaying PD progression [70, 85, 181–183].

The CB1 receptor antagonists can also influence movement syndromes of Parkinson's disease suggesting that modulation of the CB1 signaling system might be valuable in treatment of motor disorders. In a study with PD rats rimobabant (SR141716A), a selective antagonist of CB1 receptors has shown the potential to act as an antihypokinetic agent by enhancing glutamate release from excitatory afferents to the striatum [184]. Moreover, SR141716A prevented the effects of THC on dopamine release [156, 167] and also increased the locomotor activity in mice and rats preexposed to THC [170, 185]. SR141716A produced a 71% increase in motor activity in MPTP-lesioned marmosets with LID [136]. Coadministration of SR141716A with levodopa resulted in significantly less dyskinesia than administration of levodopa alone [136, 160]. SR141716A also reversed effect of the cannabinoid agonist WIN 55,212-2 and increased the locomotor activity in 6-OHDA-lesioned animals [159, 163]. Coadministration of SR141716A with a selective D₂/D₃ receptor agonist quinpirole reduced levels of AEA and 2AG by sevenfold in the globus pallidus, boosted the locomotive effects of quinpirole, and produced restoration of locomotion in animal models of Parkinson's disease [98, 99, 101, 136, 186]. In parkin-null mice SR141716A produced a decrease in tyrosine hydroxylase activity in the caudate-putamen and as result formed a hyperkinetic response [122]. However, SR141716A did not alleviate the motor deficits in a primate model of Parkinson's disease [125].

Another CB1 receptor antagonist AM251 and SR141716A produced antiparkinsonian effects in rats with very severe nigral degeneration (>95% cell loss) [187]. Local administration of these antagonists into denervated striatum, globus pallidus, and subthalamic nucleus reduced motor asymmetry in Parkinsonian rats [187, 188], which was inhibited by CB1 receptor agonist AM404 [187]. Another CB1 antagonist CE-178253 produced a 30% increase in motor behavior responses to L-DOPA in MPTP-treated rhesus monkeys but did not modify levodopa-induced dyskinesias [189]. THCV caused changes in glutamatergic transmission and attenuated the motor inhibition in PD rats [70]. Overall, these findings suggest that cannabinoid CB1 antagonists might be therapeutically effective in the control of Parkinson's disease and levodopa-induced dyskinesia [114, 190].

The activation of CB2 receptors might also contribute to some extent to the potential of cannabinoids in PD [191]. THCV, which is not only a CB1 antagonist but also a CB2 partial agonist, reduced the loss of tyrosine hydroxylase-positive neurons in the substantia nigra with preservation of these neurons in CB2 receptor-deficient mice [70]. CBD has also reduced the loss of tyrosine hydroxylase-positive neurons in the substantia nigra of PD rats. Both compounds, THCV and CBD, have acted via neuroprotective and antioxidant mechanisms [70, 182, 191]. CBD has also demonstrated significant effects in preclinical models of neurodegenerative disorders in combination with other cannabinoids [15, 70, 192]. CB2 receptor agonists display a promising pharmacological profile for delaying disease progression.

The cannabinoid pharmacologic manipulation represents a promising therapy to alleviate movement disorders and levodopa-induced dyskinesias. Thus, CB1 antagonists appear to have antiparkinsonian effects, while cannabinoid receptor agonists may be useful in the treatment of motor complications in Parkinson's disease.

3.3. Effect of Cannabinoids on Patients with Movement Disorders. Cannabis and related compounds have created significant research interest as a promising therapy in neurodegenerative and movement disorders. The successful use of tincture of *Cannabis indica* in treating PD was first described in Europe by Gowers [193]. Despite the lack of controlled studies, there is evidence that cannabinoids are of therapeutic value in the treatment of tics in Tourette syndrome, some forms of tremor and dystonia, chorea in Huntington's disease, the reduction of levodopa-induced dyskinesia in Parkinson's disease, and Parkinsonian syndromes [194–201].

A study with smoked cannabis queried 339 PD patients indicated that marijuana produced significant improvement of general PD symptoms in 46% of the patients; 31% of them reported improvement in resting tremor, 38% reported relief from rigidity, 45% defined reduced bradykinesia, and 14% of the patients reported alleviated dyskinesias [202]. High urine concentration (>50 ng/ml) of the THC primary active metabolite, 11-HO-THC, was associated with relief from PD symptoms [202]. The dose and frequency of the cannabis administrations were important in relieving PD symptoms. Smoked cannabis also produced a statistically significant improvement in tremor, rigidity, and bradykinesia as well as improvement in sleep and pain scores in 22 PD patients [65]. In another study, smoked cannabis was responsible for a significant improvement in the mean total motor Unified Parkinson's Disease Rating Scale (UPDRS) score, tremor, rigidity, and bradykinesia in 17 patients with PD [203]. One dose of smoked marijuana provided symptoms relief for up to 3 hours [203]. Moreover, both studies reported significant improvement of nonmotor symptoms of PD, such as pain and sleep [65, 203]. However, smoked marijuana did not reduce Parkinsonian symptoms in 5 patients with idiopathic Parkinson's disease and severe tremor [204]. A clinical trial in 19 PD and 6 patients with levodopa-induced dyskinesia demonstrated that oral cannabis extract was ineffective for alleviating parkinsonism or dyskinesia [205].

Few studies have evaluated the effects of CBD on PD symptoms. In a pilot study CBD lowered total UPDRS scores and significantly reduced psychotic symptoms in 6 PD patients with psychosis [67]. In another study CBD administration produced no improvement in measures of motor and general symptoms in 21 PD patients [68, 69]. However, the group treated with CBD had significantly different mean total scores in the Parkinson's Disease Questionnaire, 39 compared to the placebo group [68, 69]. Oral CBD improved dyskinesia by up to 30% without a significant worsening of the parkinsonism in PD patients [206]. CBD withdrawal caused severe generalized dystonia [206].

Clinical studies have been conducted to evaluate the effect of a synthetic cannabinoid nabilone. Oral nabilone significantly reduced dyskinesia without aggravating parkinsonism in seven PD patients with severe L-DOPA-induced dyskinesia [207]. In another study, nabilone produced a 22% reduction in levodopa-induced dyskinesia in PD patients [208]. Nabilone showed efficacy not only against LID but also against bradykinesia in PD patients [209]. Some other cannabinoid related compounds such as CE178253, OEA, and HU-210 have also been reported to be efficacious against L-DOPA-induced dyskinesia and bradykinesia in PD [199, 209]. However, SR 141716 did not improve Parkinsonian motor disability in PD patients [210]. The American Academy of Neurology (AAN) review deemed marijuana "probably ineffective" for treating L-DOPA-induced dyskinesia [211]. These conflicting results indicate the need for more research in this area.

Several clinical studies have been performed to evaluate the effect of marijuana on dystonia. Inhaled cannabis has provided a marked reduction in dystonia and complete pain relief in patients with right hemiplegic painful dystonia. Moreover, the patients have been able to completely discontinue opioid use [212]. Smoked cannabis also improved idiopathic dystonia and generalized dystonia due to Wilson's disease [213, 214]. In a preliminary study, administration of CBD resulted in a 50% improvement in spasm severity and frequency in a patient with blepharospasm- oromandibular dystonia [215] and amelioration of the dystonic movements within 2-3 hours in patients with dystonic movement disorders [201]. CBD also improved dystonia by 20-50% in dystonic patients and stopped tremor and hypokinesia in 2 patients with Parkinson's disease [200]. Another cannabis compound, THC, produced a reduction of abnormal movement patterns in a 14-year-old girl with marked dystonia [216] and decreased intensity of myoclonic movements in a 13-year-old boy with athetosis and myoclonic movements [216]. In contrast to these findings, one study found no significant reduction in dystonia following treatment with nabilone [165, 166].

Studies have looked at the potential benefits of medical marijuana and cannabinoids for the treatment of Huntington's disease (HD). Nabilone versus placebo showed a treatment difference of 0.86 for total motor score; 1.68 for chorea; 3.57 for Unified Huntington's Disease Rating Scale (UHDRS) cognition; 4.01 for UHDRS behavior; and 6.43 for the neuropsychiatric inventory in HD patients [217]. However, in previous study nabilone was found to increase

choreatic movements in patients with HD [197, 198]. AAN guideline examining the efficacy of marijuana for treating chorea in HD stated nabilone can be used for modest decreases in HD chorea [218]. Available data regarding the effect of CBD on HD symptoms are inconsistent. CBD produced improvement (20-40%) in the choreic movements in HD patients [219]. However, a latter study did not confirm the earlier finding [220]. A comparison of the effects of CBD and placebo on chorea severity in neuroleptic-free HD patients indicated no significant or clinically important differences [220].

Few studies have indicated that marijuana and THC can reduce tics and associated behavioral disorders in patients with Tourette's syndrome (TS) [221]. Cannabis inhalations produced a significant amelioration of TS symptoms [222]. Following marijuana administration 82% of TS patients ($N = 64$) reported a reduction, or complete remission of motor and vocal tics, and an amelioration of premonitory urges and obsessive-compulsive symptoms (OCB) [199]. Smoked marijuana also eliminated TS symptoms in one case study [223]. Administration of THC to a boy with TS improved tics and enhanced short-interval intracortical inhibition and the prolongation of the cortical silent period [224]. TCH significantly reduced tics and improve driving ability in a Tourette's patient [225]. Treatment with THC lowered the mean $C1$ specific over nonspecific binding ratio (V_3'') from 0.30 to 0.25 in six TS patients, although the difference was not significant. However V_3'' clearly declined in a patient with a marked clinical response [226]. To date, there have been only two controlled trials that investigated the effect of THC on TS [194], both of which reported a significant improvement of tics and OCB after THC administration [195, 196].

Considering the relevance of these data, the need for alternative treatments for PD motor and nonmotor symptoms, medical marijuana, or related compounds may provide a new approach to the treatment of Parkinson's disease.

4. Beneficial Effects of Cannabinoids in the Amelioration of Nonmotor Symptoms and Progression of Parkinson's Disease

4.1. Neuroprotective Actions of Cannabinoids. Cannabinoids have been shown to have neuroprotective effect due to their antioxidative, anti-inflammatory actions and their ability to suppress excitotoxicity. Plant-derived cannabinoids such as THC and CBD can provide neuroprotection against the in vivo and in vitro toxicity of 6-hydroxydopamine and this was thought to be due to their antioxidative property or modulation of glial cell function or a combination of both [182]. Studies found that CBD was able to recover 6-hydroxydopamine-induced dopamine depletion and also induced upregulation of Cu, Zn-superoxide dismutase, which is a key enzyme in endogenous defense against oxidative stress [70, 191, 227]. The reported data suggest that CBD also diminishes the increase in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase expression and decreases the markers of oxidative stress, inflammation, and cell death in the kidneys [228]. Another study has also emphasized a role for

superoxide anion produced by microglial NADPH oxidase in augmenting the demise of dopaminergic neurons in the PD brain [229]. The mechanism by which CBD acts to reduce NADPH oxidase expression and inhibit oxidative injury within the PD brain has yet to be confirmed but it seems to act through mechanisms independent of CB1 or CB2 receptors [76]. However, data obtained from recent studies have hinted towards a direct relationship between the CB1 receptor and mitochondrial functions in the brain [230]. The phenolic ring moieties in cannabinoids display antioxidant activity guarding against glutamate-induced neurotoxicity in a cellular model [231]. CBD produced reduction of hydroperoxide-induced oxidative damage and was more protective against glutamate neurotoxicity compared to ascorbate and α -tocopherol, indicating that CBD is a potent antioxidant [232]. Taken together, these discoveries support the hypothesis that treatment with cannabinoids having antioxidant effects may modulate mitochondrial reactive oxygen species production [233] in the PD brain.

Inflammation has been shown to be a crucial pathological factor responsible for the demise of dopaminergic neurons in PD [234–236]. Glial cells appear to play a key role in neuroinflammation, since higher levels of activated microglia are reported in the substantia nigra of patients with PD compared to brains of control subjects [237, 238]. Cannabinoids demonstrate anti-inflammatory activities by suppressing toxic cytokine release and microglia activation [181–183]. Increased CB2 receptor expression in nigral cells and stimulation of these receptors protect dopaminergic neurons from microglia-induced inflammation and regulate neuronal survival [70]. The cannabinoids are known to be able to activate the CB2 receptor, which mediate the anti-inflammatory effects of the compounds and preserve cells from excessive apoptosis. Recent evidence substantiates that some cannabinoids may attenuate the neuroinflammation associated with PD [191, 239–241]. Several studies showed that CBD has anti-inflammatory properties [242–246] and can produce beneficial effect in acute inflammation and chronic neuropathic states [5, 247, 248]. THC demonstrates anti-inflammatory effect via activation of the CB1 receptor [249–251]. In addition, cannabinoids provide anti-inflammation effect by reducing the vasoconstriction and restoring blood supply to the injured area [252]. All these data support that cannabinoids are potentially effective compounds for the treatment of neuroinflammatory conditions, including neurodegenerative diseases like PD.

Marijuana may prevent brain damage by protecting against neuronal injury. There are a few mechanisms by which cannabinoids provide neuroprotection. One of the mechanisms involves an induction/upregulation of cannabinoid CB2 receptors, mainly in reactive microglia, and regulates the influence of these glial cells on homeostasis of surrounding neurons [253]. In combination with the increased antitoxic effects observed in cell cultures containing glia, this suggests that immunomodulation produced by CB2 receptor activation may play a primary role in the neuroprotective properties of cannabinoids [182]. Another mechanism of neuroprotection is activation of CB1 receptors. Loss of dopaminergic neurons and greater degree of motor impairment in

CB1 knockout mice have been reported [85]. Cannabinoids activating the CB1 receptor are antiexcitotoxic due to suppression of glutamatergic activity with a subsequent decrease in calcium ion influx and eventual nitric oxide production [254–256]. Sativex-like combination of phytocannabinoids has been demonstrated to produce neuroprotective effect via interaction with both CB1 and CB2 receptors [134, 257]. In addition, THC reduced the loss of tyrosine hydroxylase-positive neurons in the substantia nigra [70] and exhibited neuroprotective effect by activation of the PPAR γ receptors [258]. Overall, these data suggest that cannabinoids are neuroprotective in acute and chronic neurodegeneration and can delay or even stop progressive degeneration of brain dopaminergic system, a process that cannot be prevented currently.

4.2. Analgesic Effect of Cannabinoids. Pain is a relevant and often underestimated nonmotor symptom of PD [259, 260]. Pain affects more than 50% of people with this disorder and can cause extreme physical, psychological, and social disorders and worsen Parkinsonian disability [261, 262]. Different treatment options are used to treat PD pain [262–265]. However, these medications have significant side effects and do not provide universal efficacy [264, 265]. Cannabis is well known as a pain-relieving plant. The cannabinoid receptors in the central and peripheral nervous systems have been shown to modulate pain perception [266, 267].

Several clinical studies have been performed to investigate the effect of marijuana or cannabinoids on pain. Smoked cannabis significantly reduced neuropathic pain intensity as well as significantly improved mood disturbance, physical disability, and quality of life in HIV-patients [268]. Cannabis was effective at ameliorating neuropathic pain in patients with central and peripheral neuropathic pain [269]. Inhaled cannabis significantly reduced pain intensity (34%) compared to placebo in a clinical trial of painful distal symmetric polyneuropathy (DSPN) [270]. Whole plant extracts of *Cannabis sativa* produced statistically significant improvements on the mean pain severity score [271]. Cannabis-based medicine significantly decreased chronic pain intensity as well as sleep disturbance in multiple sclerosis patients [272, 273]. Oromucosal nabiximols (1:1 combination of the THC and CBD) produced a reduction in pain intensity scores in patients with neuropathic pain [274].

These findings are consistent with other discoveries supporting the efficacy of cannabis in relieving pain. The analgesic effect of cannabinoids has been reviewed [75, 211, 275–281]. The review of the literature suggests that marijuana and/or cannabinoids may be efficacious for pain relieving in various disease states including PD.

4.3. Antidepressant Effect of Cannabinoids. Depression is one of the common nonmotor symptoms of PD and the estimated rate varies widely, with an average prevalence of up to 50%. [282–284]. Despite its association with poor health outcomes and quality of life, depression in PD patients is underdiagnosed and undertreated [285–287]. Studies have indicated that the endocannabinoid system is involved in

the regulation of mood and emotional behavior, and the loss or blockade of the endocannabinoid signaling system results in depressive symptoms [288]. For example, the CB1 receptor antagonist rimonabant has been shown to induce symptoms of anxiety and depression [289–291]. In addition, polymorphism of the gene that encodes the CB1 receptor has been associated with depression in PD [292]. In animal models, low level of THC produced antidepressant activity and increased serotonergic activity via activation of the CB1 receptor [293]. Animal studies have also shown that inhibition of hydrolysis of the endocannabinoid anandamide exerts antidepressant effect [294] and resulted in an increased serotonergic and noradrenergic neuronal activity in the midbrain. Currently available antidepressant drugs act via increasing serotonin and/or noradrenaline levels. These, and many other studies, indicate that the cannabinoid system is a potential target for the development of novel antidepressant drugs. Epidemiological studies have demonstrated that people who used cannabis daily or weekly exhibit less depressed mood and more positive effect than nonusers of cannabis [295]. Other studies have shown an association between heavy cannabis use and depressive symptoms. However, it is not clear whether the increased depressive symptoms are due to cannabis use or other factors that increased the risk of both depression and heavy use of cannabis [296]. Therefore, moderate use of cannabis in PD patients may help alleviate depressive symptoms and improve quality of life.

4.4. Effect of Cannabinoids on Sleep Disorders. Sleep disorders are common in PD patients and negatively affect the quality of life. The reported prevalence ranges from 25% to 98% and this wide variation could be due to differences in study design and diagnostic tools used [297]. The causes of the sleep disturbances in PD are multifactorial and include neurodegeneration and the medications used to treat motor symptoms of PD [298]. Various sleep disorders including rapid eye movement sleep behavior disorder, insomnia, sleep fragmentation, excessive daytime sleepiness, restless legs syndrome, and obstructive sleep apnea have been described in PD patients [299, 300]. Cannabidiol, the major nonpsychotic component of marijuana, has been reported to improve rapid eye movement sleep behavior disorder in PD patients [68, 69]. Marijuana has also been shown to improve nonmotor symptoms of PD including sleep [65]. In clinical trials involving 2000 patients with various pain conditions, nabiximols has been demonstrated to improve subjective sleep parameters [301]. Thus, marijuana could be used to enhance the quality of life of PD patients by alleviating sleep disorders and pain.

5. Summary

Cannabis and related compounds have recently been studied as promising therapeutic agents in treatment of neurodegenerative and movement disorders including Parkinson's disease. In this review we have examined the potential benefits of medical marijuana and cannabinoids in the treatment of both motor and nonmotor symptoms as well as

in slowing the progression of the disease. We have looked into any scientific evidence that indicates the potential use of marijuana and/or related compounds for the treatment of PD. Current treatments of PD provide only relief of motor symptoms and are associated with adverse effects such as dyskinesia. In addition, these therapies do not slow the progression of the disease. Therefore, there is an urgent need for safer drugs that can treat both motor and nonmotor symptoms of PD as well as drugs that slow the progression of the disease.

In spite of the placement of marijuana in schedule 1 category under the US Federal Controlled Substance Act, 24 states and Washington DC have enacted laws allowing the use of marijuana to treat a range of medical conditions. Parkinson's disease has been listed as one of the disease conditions for which medical marijuana is allowed in a number of states. Research studies have provided evidence for the potential effectiveness of medical marijuana and its components in the treatment of PD as cannabinoids act on the same neurological pathway that is disrupted in Parkinson's disease. Involvement of the endocannabinoid system in the regulation of motor behavior, the localization of the cannabinoid receptors in areas that control movement, and the effect of cannabinoids on motor activity indicate that cannabinoids can be potentially used in the treatment of movement disorders. Cannabinoid agonists and antagonists have been shown to modulate the endocannabinoid system and modify motor activity. Cannabinoid receptor antagonists appear to produce antiparkinsonian effects while cannabinoid receptor agonists exert a powerful motor inhibition and may be useful in the treatment of motor complications. In addition, we have assessed the role of the cannabinoid system and marijuana constituents in neuroprotection as well as considered other beneficial effects of marijuana. Marijuana has been shown to improve nonmotor symptoms of PD such as depression, pain, sleep, and anxiety. Moreover, components of cannabis have been demonstrated to have neuroprotective effect due to their anti-inflammatory, antioxidative, and antiexcitotoxic properties. Due to combination of the above mentioned beneficial effects, cannabis may provide a viable alternative or addition to the current treatment of Parkinson's disease. However, there are concerns regarding the use of medical marijuana including lack of standardization and regulation, imprecise dosing, possible adverse effects, and medication interactions. Further studies are needed to provide more data on efficacy, safety, pharmacokinetics, and interactions of cannabinoids.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

- [1] L. M. Borgelt, K. L. Franson, A. M. Nussbaum, and G. S. Wang, "The pharmacologic and clinical effects of medical cannabis," *Pharmacotherapy*, vol. 33, no. 2, pp. 195–209, 2013.

- [2] M. A. ElSohly and D. Slade, "Chemical constituents of marijuana: the complex mixture of natural cannabinoids," *Life Sciences*, vol. 78, no. 5, pp. 539–548, 2005.
- [3] E. B. Russo, "Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects," *British Journal of Pharmacology*, vol. 163, no. 7, pp. 1344–1364, 2011.
- [4] E. J. Rahn and A. G. Hohmann, "Cannabinoids as Pharmacotherapies for neuropathic pain: from the bench to the bedside," *Neurotherapeutics*, vol. 6, no. 4, pp. 713–737, 2009.
- [5] A. W. Zuardi, "Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action," *Revista Brasileira de Psiquiatria*, vol. 30, no. 3, pp. 271–280, 2008.
- [6] F. M. Leweke, D. Piomelli, F. Pahlisch et al., "Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia," *Translational Psychiatry*, vol. 2, no. 3, article e94, 2012.
- [7] DEA (Drug Enforcement Administration), Drug Fact Sheet: Marijuana, http://www.dea.gov/druginfo/drug_data_sheets/Marijuana.pdf.
- [8] ONDCP (Office of National Drug Control Policy), Marijuana Resource Center: State Laws Related to Marijuana, <https://www.whitehouse.gov/ondcp/state-laws-related-to-marijuana>.
- [9] Y. Park, "Georgia Regents University. Epidiolex and Drug Resistant Epilepsy in Children (CBD)," In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). NLM Identifier: NCT02397863, <https://clinicaltrials.gov/ct2/show/NCT02397863>.
- [10] W. Notcutt, R. Langford, P. Davies, S. Ratcliffe, and R. Potts, "A placebo-controlled, parallel-group, randomized withdrawal study of subjects with symptoms of spasticity due to multiple sclerosis who are receiving long-term Sativex (nabiximols)," *Multiple Sclerosis Journal*, vol. 18, no. 2, pp. 219–228, 2012.
- [11] A. Novotna, J. Mares, S. Ratcliffe et al., "A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols" (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis," *European Journal of Neurology*, vol. 18, no. 9, pp. 1122–1131, 2011.
- [12] F. Grotenhermen and K. Müller-Vahl, "The therapeutic potential of cannabis and cannabinoids," *Deutsches Arzteblatt International*, vol. 109, no. 29–30, pp. 495–501, 2012.
- [13] C. Scuderi, D. De Filippis, T. Iuvone, A. Blasio, A. Steardo, and G. Esposito, "Cannabidiol in medicine: a review of its therapeutic potential in CNS disorders," *Phytotherapy Research*, vol. 23, no. 5, pp. 597–602, 2009.
- [14] T. Iuvone, G. Esposito, D. De Filippis, C. Scuderi, and L. Steardo, "Cannabidiol: a promising drug for neurodegenerative disorders?" *CNS Neuroscience and Therapeutics*, vol. 15, no. 1, pp. 65–75, 2009.
- [15] A. J. Hill, C. M. Williams, B. J. Whalley, and G. J. Stephens, "Phytocannabinoids as novel therapeutic agents in CNS disorders," *Pharmacology and Therapeutics*, vol. 133, no. 1, pp. 79–97, 2012.
- [16] P. Fusar-Poli, J. A. Crippa, S. Bhattacharyya et al., "Distinct effects of Δ^9 -tetrahydrocannabinol and cannabidiol on neural activation during emotional processing," *Archives of General Psychiatry Journal*, vol. 66, no. 1, pp. 95–105, 2009.
- [17] D. T. Malone, M. N. Hill, and T. Rubino, "Adolescent cannabis use and psychosis: epidemiology and neurodevelopmental models," *British Journal of Pharmacology*, vol. 160, no. 3, pp. 511–522, 2010.
- [18] G. Gerra, A. Zaimovic, M. L. Gerra et al., "Pharmacology and toxicology of cannabis derivatives and endocannabinoid agonists," *Recent Patents on CNS Drug Discovery*, vol. 5, no. 1, pp. 46–52, 2010.
- [19] T. H. Moore, S. Zammit, A. Lingford-Hughes et al., "Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review," *The Lancet*, vol. 370, no. 9584, pp. 319–328, 2007.
- [20] M. G. Bossong and R. J. M. Niesink, "Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia," *Progress in Neurobiology*, vol. 92, no. 3, pp. 370–385, 2010.
- [21] M. Schneider, "Puberty as a highly vulnerable developmental period for the consequences of cannabis exposure," *Addiction Biology*, vol. 13, no. 2, pp. 253–263, 2008.
- [22] F. Grotenhermen, "The toxicology of cannabis and cannabis prohibition," *Chemistry & Biodiversity*, vol. 4, no. 8, pp. 1744–1769, 2007.
- [23] F. R. de Fonseca, I. del Arco, F. J. Bermudez-Silva, A. Bilbao, A. Cippitelli, and M. Navarro, "The endocannabinoid system: physiology and pharmacology," *Alcohol and Alcoholism*, vol. 40, no. 1, pp. 2–14, 2005.
- [24] P. Pacher, S. Bátkai, and G. Kunos, "The endocannabinoid system as an emerging target of pharmacotherapy," *Pharmacological Reviews*, vol. 58, no. 3, pp. 389–462, 2006.
- [25] T. Morera-Herreras, C. Miguelez, A. Aristieta, J. A. Ruiz-Ortega, and L. Ugedo, "Endocannabinoid modulation of dopaminergic motor circuits," *Frontiers in Pharmacology*, vol. 3, article 110, 2012.
- [26] A. El Manira and A. Kyriakatos, "The role of endocannabinoid signaling in motor control," *Physiology*, vol. 25, no. 4, pp. 230–238, 2010.
- [27] J. Fernández-Ruiz and S. González, "Cannabinoid control of motor function at the Basal Ganglia," *Handbook of Experimental Pharmacology*, vol. 168, pp. 479–507, 2005.
- [28] J. Xu, K. D. Kochanek, and S. L. Murphy, "National vital statistics reports deaths: final data for 2007," *Statistics*, vol. 58, no. 3, p. 135, 2010.
- [29] T. Pringsheim, N. Jette, A. Frolkis, and T. D. L. Steeves, "The prevalence of Parkinson's disease: a systematic review and meta-analysis," *Movement Disorders*, vol. 29, no. 13, pp. 1583–1590, 2014.
- [30] E. R. Dorsey, R. Constantinescu, J. P. Thompson et al., "Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030," *Neurology*, vol. 68, no. 5, pp. 384–386, 2007.
- [31] L. C. S. Tan, "Epidemiology of parkinson's disease," *Neurology Asia*, vol. 18, no. 3, pp. 231–238, 2013.
- [32] A. Galvan and T. Wichmann, "Pathophysiology of Parkinsonism," *Clinical Neurophysiology*, vol. 119, no. 7, pp. 1459–1474, 2008.
- [33] L. C. Kwan and T. L. Whitehill, "Perception of speech by individuals with Parkinson's disease: a review," *Parkinson's Disease*, vol. 2011, Article ID 389767, 11 pages, 2011.
- [34] B. Thomas and M. F. Beal, "Parkinson's disease," *Human Molecular Genetics*, vol. 16, no. 2, pp. R183–R194, 2007.
- [35] G. E. Alexander, "Biology of Parkinson's disease: pathogenesis and pathophysiology of a multisystem neurodegenerative disorder," *Dialogues in Clinical Neuroscience*, vol. 6, no. 3, pp. 259–280, 2004.
- [36] W. Dauer and S. Przedborski, "Parkinson's disease: mechanisms and models," *Neuron*, vol. 39, no. 6, pp. 889–909, 2003.

- [37] M. C. Rodriguez-Oroz, M. Jahanshahi, P. Krack et al., "Initial clinical manifestations of Parkinson's disease: features and pathophysiological mechanisms," *The Lancet Neurology*, vol. 8, no. 12, pp. 1128–1139, 2009.
- [38] T. Patel and F. Chang, "Parkinson's disease guidelines for pharmacists," *Canadian Pharmacists Journal*, vol. 147, no. 3, pp. 161–170, 2014.
- [39] K. R. Chaudhuri, D. G. Healy, and A. H. V. Schapira, "Non-motor symptoms of Parkinson's disease: diagnosis and management," *The Lancet Neurology*, vol. 5, no. 3, pp. 235–245, 2006.
- [40] B. Müller, J. Assmus, K. Herlofson, J. P. Larsen, and O.-B. Tysnes, "Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease," *Parkinsonism and Related Disorders*, vol. 19, no. 11, pp. 1027–1032, 2013.
- [41] J. Latoo, M. Mistry, and F. J. Dunne, "Often overlooked neuropsychiatric syndromes in Parkinson's disease," *British Journal of Medical Practitioners*, vol. 6, no. 1, pp. 23–30, 2013.
- [42] F. Stocchi, G. Abbruzzese, R. Ceravolo et al., "Prevalence of fatigue in Parkinson disease and its clinical correlates," *Neurology*, vol. 83, no. 3, pp. 215–220, 2014.
- [43] D. C. Velseboer, R. J. de Haan, W. Wieling, D. S. Goldstein, and R. M. A. de Bie, "Prevalence of orthostatic hypotension in Parkinson's disease: a systematic review and meta-analysis," *Parkinsonism and Related Disorders*, vol. 17, no. 10, pp. 724–729, 2011.
- [44] B. Connolly and S. H. Fox, "Treatment of cognitive, psychiatric, and affective disorders associated with Parkinson's disease," *Neurotherapeutics*, vol. 11, no. 1, pp. 78–91, 2014.
- [45] P. Huot, S. H. Fox, and J. M. Brotchie, "Monoamine reuptake inhibitors in Parkinson's disease," *Parkinson's Disease*, vol. 2015, Article ID 609428, 71 pages, 2015.
- [46] F. Gasparini, T. Di Paolo, and B. Gomez-Mancilla, "Metabotropic glutamate receptors for Parkinson's disease therapy," *Parkinson's Disease*, vol. 2013, Article ID 196028, 11 pages, 2013.
- [47] C. G. Goetz and G. Pal, "Initial management of Parkinson's disease," *British Medical Journal*, vol. 349, Article ID 6258, 2014.
- [48] A. Lees, "Alternatives to levodopa in the initial treatment of early Parkinson's disease," *Drugs and Aging*, vol. 22, no. 9, pp. 731–740, 2005.
- [49] R. Katzenschlager, C. Sampaio, J. Costa, and A. Lees, "Anticholinergics for symptomatic management of Parkinson's disease," *Cochrane Database of Systematic Reviews*, no. 2, Article ID CD003735, 2003.
- [50] S. Maranis, S. Tsouli, and S. Konitsiotis, "Treatment of motor symptoms in advanced Parkinson's disease: a practical approach," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 35, no. 8, pp. 1795–1807, 2011.
- [51] R. Heumann, R. Moratalla, M. T. Herrero et al., "Dyskinesia in Parkinson's disease: mechanisms and current non-pharmacological interventions," *Journal of Neurochemistry*, vol. 130, no. 4, pp. 472–489, 2014.
- [52] M. Politis, K. Wu, C. Loane et al., "Serotonergic mechanisms responsible for levodopa-induced dyskinesias in Parkinson's disease patients," *The Journal of Clinical Investigation*, vol. 124, no. 3, pp. 1340–1349, 2014.
- [53] G. Porras, P. De Deurwaerdere, Q. Li et al., "L-dopa-induced dyskinesia: beyond an excessive dopamine tone in the striatum," *Scientific Reports*, vol. 4, article 3730, 2014.
- [54] J. J. Chen, D. M. Swope, and K. Dashtipour, "Comprehensive review of rasagiline, a second-generation monoamine oxidase inhibitor, for the treatment of Parkinson's Disease," *Clinical Therapeutics*, vol. 29, no. 9, pp. 1825–1849, 2007.
- [55] S. Lecht, S. Haroutiunian, A. Hoffman, and P. Lazarovici, "Rasagiline—a novel MAO B inhibitor in Parkinson's disease therapy," *Therapeutics and Clinical Risk Management*, vol. 3, no. 3, pp. 467–474, 2007.
- [56] R. Pahwa, S. A. Factor, K. E. Lyons et al., "Practice parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology," *Neurology*, vol. 66, no. 7, pp. 983–995, 2006.
- [57] F. Stocchi and J. M. Rabey, "Effect of rasagiline as adjunct therapy to levodopa on severity of OFF in Parkinson's disease," *European Journal of Neurology*, vol. 18, no. 12, pp. 1373–1378, 2011.
- [58] O. Rascol, D. J. Brooks, E. Melamed et al., "Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomised, double-blind, controlled trial," *The Lancet Neurology*, vol. 365, pp. 947–954, 2005.
- [59] E. Tolosa and M. B. Stern, "Efficacy, safety and tolerability of rasagiline as adjunctive therapy in elderly patients with Parkinson's disease," *European Journal of Neurology*, vol. 19, no. 2, pp. 258–264, 2012.
- [60] O. Rascol, D. J. Brooks, A. D. Korczyn, P. P. De Deyn, C. E. Clarke, and A. E. Lang, "A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa," *The New England Journal of Medicine*, vol. 342, no. 20, pp. 1484–1491, 2000.
- [61] Parkinson Study Group, "Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomized controlled trial. Parkinson Study Group," *The Journal of the American Medical Association*, vol. 284, no. 15, pp. 1931–1938, 2000.
- [62] S. Perez-Lloret, M. V. Rey, P. L. Ratti, and O. Rascol, "Rotigotine transdermal patch for the treatment of Parkinson's disease," *Fundamental and Clinical Pharmacology*, vol. 27, no. 1, pp. 81–95, 2013.
- [63] J.-P. Elshoff, W. Cawello, J.-O. Andreas, F.-X. Mathy, and M. Braun, "An update on pharmacological, pharmacokinetic properties and drug-drug interactions of rotigotine transdermal system in Parkinson's disease and restless legs syndrome," *Drugs*, vol. 75, no. 5, pp. 487–501, 2015.
- [64] D. Deleu, Y. Hanssens, and M. G. Northway, "Subcutaneous apomorphine: an evidence-based review of its use in Parkinson's disease," *Drugs and Aging*, vol. 21, no. 11, pp. 687–709, 2004.
- [65] I. Lotan, T. A. Treves, Y. Roditi, and R. Djaldetti, "Cannabis (medical marijuana) treatment for motor and non-motor symptoms of Parkinson disease," *Clinical Neuropharmacology*, vol. 37, no. 2, pp. 41–44, 2014.
- [66] T. A. Finseth, J. L. Hedeman, R. P. Brown, K. I. Johnson, M. S. Binder, and B. M. Kluger, "Self-reported efficacy of cannabis and other complementary medicine modalities by Parkinson's disease patients in Colorado," *Evidence-Based Complementary and Alternative Medicine*, vol. 2015, Article ID 874849, 6 pages, 2015.
- [67] A. W. Zuardi, J. A. S. Crippa, J. E. C. Hallak et al., "Cannabidiol for the treatment of psychosis in Parkinson's disease," *Journal of Psychopharmacology*, vol. 23, no. 8, pp. 979–983, 2009.
- [68] M. H. N. Chagas, A. W. Zuardi, V. Tumas et al., "Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial," *Journal of Psychopharmacology*, vol. 28, no. 11, pp. 1088–1092, 2014.

- [69] M. H. N. Chagas, A. L. Eckeli, A. W. Zuardi et al., "Cannabidiol can improve complex sleep-related behaviours associated with rapid eye movement sleep behaviour disorder in Parkinson's disease patients: a case series," *Journal of Clinical Pharmacy and Therapeutics*, vol. 39, no. 5, pp. 564–566, 2014.
- [70] C. García, C. Palomo-Garo, M. García-Arencibia, J. A. Ramos, R. G. Pertwee, and J. Fernández-Ruiz, "Symptom-relieving and neuroprotective effects of the phytocannabinoid Δ^9 -THCV in animal models of Parkinson's disease," *British Journal of Pharmacology*, vol. 163, no. 7, pp. 1495–1506, 2011.
- [71] M. Shen and S. A. Thayer, " Δ^9 -Tetrahydrocannabinol acts as a partial agonist to modulate glutamatergic synaptic transmission between rat hippocampal neurons in culture," *Molecular Pharmacology*, vol. 55, no. 1, pp. 8–13, 1999.
- [72] R. Murase, R. Kawamura, E. Singer et al., "Targeting multiple cannabinoid anti-tumour pathways with a resorcinol derivative leads to inhibition of advanced stages of breast cancer," *British Journal of Pharmacology*, vol. 171, no. 19, pp. 4464–4477, 2014.
- [73] O. Devinsky, M. R. Cilio, H. Cross et al., "Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders," *Epilepsia*, vol. 55, no. 6, pp. 791–802, 2014.
- [74] M. Babayeva, M. Fuzailov, P. Rozenfeld, and P. Basu, "Marijuana compounds: a non-conventional therapeutic approach to epilepsy in children," *Journal of Addiction Neuropharmacology*, vol. 1, pp. 2–36, 2014.
- [75] J. L. Croxford, "Therapeutic potential of cannabinoids in CNS disease," *CNS Drugs*, vol. 17, no. 3, pp. 179–202, 2003.
- [76] J. Fernández-Ruiz, O. Sagredo, M. R. Pazos et al., "Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid?" *British Journal of Clinical Pharmacology*, vol. 75, no. 2, pp. 323–333, 2013.
- [77] Y. Hashimoto-dani, T. Ohno-Shosaku, M. Watanabe, and M. Kano, "Roles of phospholipase C β and NMDA receptor in activity-dependent endocannabinoid release," *The Journal of Physiology*, vol. 584, no. 2, pp. 373–380, 2007.
- [78] Z. Hegyi, K. Holló, G. Kis, K. Mackie, and M. Antal, "Differential distribution of diacylglycerol lipase- α and N-acylphosphatidylethanolamine-specific phospholipase d immunoreactivity in the superficial spinal dorsal horn of rats," *Glia*, vol. 60, no. 9, pp. 1316–1329, 2012.
- [79] P. G. Fine and M. J. Rosenfeld, "The endocannabinoid system, cannabinoids, and pain," *Rambam Maimonides Medical Journal*, vol. 4, no. 4, Article ID e0022, 2013.
- [80] E. M. Marco, S. Y. Romero-Zerbo, M.-P. Viveros, and F. J. Bermudez-Silva, "The role of the endocannabinoid system in eating disorders: pharmacological implications," *Behavioural Pharmacology*, vol. 23, no. 5–6, pp. 526–536, 2012.
- [81] C. R. Hiley, "Endocannabinoids and the heart," *Journal of Cardiovascular Pharmacology*, vol. 53, no. 4, pp. 267–276, 2009.
- [82] R. G. Pertwee, "The diverse CB 1 and CB 2 receptor pharmacology of three plant cannabinoids: Δ 9-tetrahydrocannabinol, cannabidiol and Δ 9-tetrahydrocannabivarin," *British Journal of Pharmacology*, vol. 153, no. 2, pp. 199–215, 2008.
- [83] J.-Y. Xu and C. Chen, "Endocannabinoids in synaptic plasticity and neuroprotection," *Neuroscientist*, vol. 21, no. 2, pp. 152–168, 2015.
- [84] V. L. Hegde, M. Nagarkatti, and P. S. Nagarkatti, "Cannabinoid receptor activation leads to massive mobilization of myeloid-derived suppressor cells with potent immunosuppressive properties," *European Journal of Immunology*, vol. 40, no. 12, pp. 3358–3371, 2010.
- [85] S. Pérez-Rial, M. S. García-Gutiérrez, J. A. Molina et al., "Increased vulnerability to 6-hydroxydopamine lesion and reduced development of dyskinesias in mice lacking CB1 cannabinoid receptors," *Neurobiology of Aging*, vol. 32, no. 4, pp. 631–645, 2011.
- [86] D. Piomelli, "The molecular logic of endocannabinoid signalling," *Nature Reviews Neuroscience*, vol. 4, no. 11, pp. 873–884, 2003.
- [87] L. A. Matsuda, S. J. Lolait, M. J. Brownstein, A. C. Young, and T. I. Bonner, "Structure of a cannabinoid receptor and functional expression of the cloned cDNA," *Nature*, vol. 346, no. 6284, pp. 561–564, 1990.
- [88] M. Herkenham, A. B. Lynn, M. D. Little et al., "Cannabinoid receptor localization in brain," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 87, no. 5, pp. 1932–1936, 1990.
- [89] I. Ivanov, P. Borchert, and B. Hinz, "A simple method for simultaneous determination of N-arachidonylethanolamine, N-oleylethanolamine, N-palmitoylethanolamine and 2-arachidonoylglycerol in human cells," *Analytical and Bioanalytical Chemistry*, vol. 407, no. 6, pp. 1781–1787, 2015.
- [90] R. G. Pertwee, A. C. Howlett, M. E. Abood et al., "International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: Beyond CB1 and CB2," *Pharmacological Reviews*, vol. 62, no. 4, pp. 588–631, 2010.
- [91] N. T. Snider, V. J. Walker, and P. F. Hollenberg, "Oxidation of the endogenous cannabinoid arachidonoyl ethanolamide by the cytochrome P450 monooxygenases: physiological and pharmacological implications," *Pharmacological Reviews*, vol. 62, no. 1, pp. 136–154, 2010.
- [92] M. W. Buczynski and L. H. Parsons, "Quantification of brain endocannabinoid levels: methods, interpretations and pitfalls," *British Journal of Pharmacology*, vol. 160, no. 3, pp. 423–442, 2010.
- [93] C. C. Felder, A. Nielsen, E. M. Briley et al., "Isolation and measurement of the endogenous cannabinoid receptor agonist, anandamide, in brain and peripheral tissues of human and rat," *FEBS Letters*, vol. 393, no. 2–3, pp. 231–235, 1996.
- [94] T. Sugiura, S. Kondo, S. Kishimoto et al., "Evidence that 2-arachidonoylglycerol but not N-palmitoylethanolamine or anandamide is the physiological ligand for the cannabinoid CB2 receptor. Comparison of the agonistic activities of various cannabinoid receptor ligands in HL-60 cells," *Journal of Biological Chemistry*, vol. 275, no. 1, pp. 605–612, 2000.
- [95] T. Bisogno, F. Berrendero, G. Ambrosino et al., "Brain regional distribution of endocannabinoids: implications for their biosynthesis and biological function," *Biochemical and Biophysical Research Communications*, vol. 256, no. 2, pp. 377–380, 1999.
- [96] R. Mechoulam, S. Ben-Shabat, L. Hanus et al., "Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors," *Biochemical Pharmacology*, vol. 50, no. 1, pp. 83–90, 1995.
- [97] W. Gonsiorek, C. Lunn, X. Fan, S. Narula, D. Lundell, and R. W. Hipkin, "Endocannabinoid 2-arachidonoyl glycerol is a full agonist through human type 2 cannabinoid receptor: antagonism by anandamide," *Molecular Pharmacology*, vol. 57, no. 5, pp. 1045–1050, 2000.
- [98] V. Di Marzo, F. Berrendero, T. Bisogno et al., "Enhancement of anandamide formation in the limbic forebrain and reduction of endocannabinoid contents in the striatum of Δ 9-

- tetrahydrocannabinol-tolerant rats," *Journal of Neurochemistry*, vol. 74, no. 4, pp. 1627–1635, 2000.
- [99] V. Di Marzo, M. P. Hill, T. Bisogno, A. R. Crossman, and J. M. Brotchie, "Enhanced levels of endogenous cannabinoids in the globus pallidus are associated with a reduction in movement in an animal model of Parkinson's disease," *FASEB Journal*, vol. 14, no. 10, pp. 1432–1438, 2000.
- [100] G. Palermo, I. Bauer, P. Campomanes et al., "Keys to lipid selection in fatty acid amide hydrolase catalysis: structural flexibility, gating residues and multiple binding pockets," *PLoS Computational Biology*, vol. 11, no. 6, article e1004231, 2015.
- [101] A. Giuffrida, L. H. Parsons, T. M. Kerr, F. Rodríguez De Fonseca, M. Navarro, and D. Piomelli, "Dopamine activation of endogenous cannabinoid signaling in dorsal striatum," *Nature Neuroscience*, vol. 2, no. 4, pp. 358–363, 1999.
- [102] L. De Petrocellis, M. G. Cascio, and V. Di Marzo, "The endocannabinoid system: a general view and latest additions," *British Journal of Pharmacology*, vol. 141, no. 5, pp. 765–774, 2004.
- [103] B. S. Basavarajappa, "Neuropharmacology of the endocannabinoid signaling system-molecular mechanisms, biological actions and synaptic plasticity," *Current Neuropharmacology*, vol. 5, no. 2, pp. 81–97, 2007.
- [104] I. G. Karniol and E. A. Carlini, "Pharmacological interaction between cannabidiol and $\delta 9$ -tetrahydrocannabinol," *Psychopharmacologia*, vol. 33, no. 1, pp. 53–70, 1973.
- [105] R. Mechoulam and Y. Shvo, "Hashish—I: the structure of cannabidiol," *Tetrahedron*, vol. 19, pp. 2073–2078, 1963.
- [106] V. Di Marzo and A. Fontana, "Anandamide, an endogenous cannabinomimetic eicosanoid: 'killing two birds with one stone,'" *Prostaglandins, Leukotrienes and Essential Fatty Acids*, vol. 53, no. 1, pp. 1–11, 1995.
- [107] H. J. Groenewegen, "The basal ganglia and motor control," *Neural Plasticity*, vol. 10, no. 1-2, pp. 107–120, 2003.
- [108] P. Calabresi, B. Picconi, A. Tozzi, V. Ghiglieri, and M. Di Filippo, "Direct and indirect pathways of basal ganglia: a critical reappraisal," *Nature Neuroscience*, vol. 17, no. 8, pp. 1022–1030, 2014.
- [109] J. Fernández-Ruiz, "The endocannabinoid system as a target for the treatment of motor dysfunction," *British Journal of Pharmacology*, vol. 156, no. 7, pp. 1029–1040, 2009.
- [110] B. D. Heifets and P. E. Castillo, "Endocannabinoid signaling and long-term synaptic plasticity," *Annual Review of Physiology*, vol. 71, pp. 283–306, 2009.
- [111] E. Bezard, J. M. Brotchie, and C. E. Gross, "Pathophysiology of levodopa-induced dyskinesia: potential for new therapies," *Nature Reviews Neuroscience*, vol. 2, no. 8, pp. 577–588, 2001.
- [112] S. V. More and D.-K. Choi, "Promising cannabinoid-based therapies for Parkinson's disease: motor symptoms to neuroprotection," *Molecular Neurodegeneration*, vol. 10, no. 1, article 17, 2015.
- [113] M. García-Arencibia, C. García, and J. Fernández-Ruiz, "Cannabinoids and Parkinson's disease," *CNS and Neurological Disorders—Drug Targets*, vol. 8, no. 6, pp. 432–439, 2009.
- [114] J. M. Brotchie, "CB1 cannabinoid receptor signalling in Parkinson's disease," *Current Opinion in Pharmacology*, vol. 3, no. 1, pp. 54–61, 2003.
- [115] M. van der Stelt and V. Di Marzo, "The endocannabinoid system in the basal ganglia and in the mesolimbic reward system: implications for neurological and psychiatric disorders," *European Journal of Pharmacology*, vol. 480, no. 1–3, pp. 133–150, 2003.
- [116] E. Benarroch, "Endocannabinoids in basal ganglia circuits: implications for Parkinson disease," *Neurology*, vol. 69, no. 3, pp. 306–309, 2007.
- [117] F. R. Fusco, A. Martorana, C. Giampà et al., "Immunolocalization of CB1 receptor in rat striatal neurons: A Confocal Microscopy Study," *Synapse*, vol. 53, no. 3, pp. 159–167, 2004.
- [118] M. Di Filippo, B. Picconi, A. Tozzi, V. Ghiglieri, A. Rossi, and P. Calabresi, "The endocannabinoid system in Parkinson's disease," *Current Pharmaceutical Design*, vol. 14, no. 23, pp. 2337–2346, 2008.
- [119] I. Lastres-Becker, M. Cebeira, M. L. De Ceballos et al., "Increased cannabinoid CB1 receptor binding and activation of GTP-binding proteins in the basal ganglia of patients with Parkinson's syndrome and of MPTP-treated marmosets," *European Journal of Neuroscience*, vol. 14, no. 11, pp. 1827–1832, 2001.
- [120] I. Lastres-Becker, F. Fezza, M. Cebeira et al., "Changes in endocannabinoid transmission in the basal ganglia in a rat model of Huntington's disease," *NeuroReport*, vol. 12, no. 10, pp. 2125–2129, 2001.
- [121] T. M. Dawson and V. L. Dawson, "Rare genetic mutations shed light on the pathogenesis of Parkinson disease," *The Journal of Clinical Investigation*, vol. 111, no. 2, pp. 145–151, 2003.
- [122] S. González, M. A. Mena, I. Lastres-Becker et al., "Cannabinoid CB₁ receptors in the basal ganglia and motor response to activation or blockade of these receptors in parkin-null mice," *Brain Research*, vol. 1046, no. 1-2, pp. 195–206, 2005.
- [123] R. I. Wilson and R. A. Nicoll, "Endocannabinoid signaling in the brain," *Science*, vol. 296, no. 5568, pp. 678–682, 2002.
- [124] J. P. Meschler, T. J. Conley, and A. C. Howlett, "Cannabinoid and dopamine interaction in rodent brain: effects on locomotor activity," *Pharmacology Biochemistry and Behavior*, vol. 67, no. 3, pp. 567–573, 2000.
- [125] J. P. Meschler, A. C. Howlett, and B. K. Madras, "Cannabinoid receptor agonist and antagonist effects on motor function in normal and 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP)-treated non-human primates," *Psychopharmacology*, vol. 156, no. 1, pp. 79–85, 2001.
- [126] L. A. Batista, P. H. Gobira, T. G. Viana, D. C. Aguiar, and F. A. Moreira, "Inhibition of endocannabinoid neuronal uptake and hydrolysis as strategies for developing anxiolytic drugs," *Behavioural Pharmacology*, vol. 25, no. 5-6, pp. 425–433, 2014.
- [127] É. Mezey, Z. E. Tóth, D. N. Cortright et al., "Distribution of mRNA for vanilloid receptor subtype 1 (VR1), and VR1-like immunoreactivity, in the central nervous system of the rat and human," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 7, pp. 3655–3660, 2000.
- [128] E. Palazzo, F. Rossi, and S. Maione, "Role of TRPV1 receptors in descending modulation of pain," *Molecular and Cellular Endocrinology*, vol. 286, no. 1-2, supplement 1, pp. S79–S83, 2008.
- [129] E. de Lago, R. de Miguel, I. Lastres-Becker, J. A. Ramos, and J. Fernández-Ruiz, "Involvement of vanilloid-like receptors in the effects of anandamide on motor behavior and nigrostriatal dopaminergic activity: in vivo and in vitro evidence," *Brain Research*, vol. 1007, no. 1-2, pp. 152–159, 2004.
- [130] T. dos Anjos-Garcia, F. Ullah, L. L. Falconi-Sobrinho, and N. C. Coimbra, "CB1 cannabinoid receptor-mediated anandamide signalling reduces the defensive behaviour evoked through GABAA receptor blockade in the dorsomedial division of the ventromedial hypothalamus," *Neuropharmacology*, vol. 113, pp. 156–166, 2016.

- [131] E. Lizanecz, Z. Bagi, E. T. Pásztor et al., "Phosphorylation-dependent desensitization by anandamide of vanilloid receptor-1 (TRPV1) function in rat skeletal muscle arterioles and in Chinese hamster ovary cells expressing TRPV1," *Molecular Pharmacology*, vol. 69, no. 3, pp. 1015–1023, 2006.
- [132] A. V. Kravitz, B. S. Freeze, P. R. L. Parker et al., "Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry," *Nature*, vol. 466, no. 7306, pp. 622–626, 2010.
- [133] A. C. Kreitzer and R. C. Malenka, "Endocannabinoid-mediated rescue of striatal LTD and motor deficits in Parkinson's disease models," *Nature*, vol. 445, no. 7128, pp. 643–647, 2007.
- [134] O. Sagredo, M. R. Pazos, V. Satta, J. A. Ramos, R. G. Pertwee, and J. Fernández-Ruiz, "Neuroprotective effects of phytocannabinoid-based medicines in experimental models of Huntington's disease," *Journal of Neuroscience Research*, vol. 89, no. 9, pp. 1509–1518, 2011.
- [135] D. E. Moss, S. B. McMaster, and J. Rogers, "Tetrahydrocannabinol potentiates reserpine-induced hypokinesia," *Pharmacology, Biochemistry and Behavior*, vol. 15, no. 5, pp. 779–783, 1981.
- [136] M. Van Der Stelt, S. H. Fox, M. Hill et al., "A role for endocannabinoids in the generation of parkinsonism and levodopa-induced dyskinesia in MPTP-lesioned non-human primate models of Parkinson's disease," *FASEB Journal*, vol. 19, no. 9, pp. 1140–1142, 2005.
- [137] T. Bisogno, F. Berrendero, G. Ambrosino et al., "Brain regional distribution of endocannabinoids: implications for their biosynthesis and biological function," *Biochemical and Biophysical Research Communications*, vol. 256, no. 2, pp. 377–380, 1999.
- [138] M. C. Sañudo-Peña, K. Tsou, and J. M. Walker, "Motor actions of cannabinoids in the basal ganglia output nuclei," *Life Sciences*, vol. 65, no. 6–7, pp. 703–713, 1999.
- [139] I. Lastres-Becker, H. H. Hansen, F. Berrendero et al., "Alleviation of motor hyperactivity and neurochemical deficits by endocannabinoid uptake inhibition in a rat model of Huntington's disease," *Synapse*, vol. 44, no. 1, pp. 23–35, 2002.
- [140] M. Glass, M. Draganow, and R. L. Faull, "The pattern of neurodegeneration in Huntington's disease: a comparative study of cannabinoid, dopamine, adenosine and GABA_A receptor alterations in the human basal ganglia in Huntington's disease," *Neuroscience*, vol. 97, no. 3, pp. 505–519, 2000.
- [141] K. Van Laere, C. Casteels, S. Lunskens et al., "Regional changes in type I cannabinoid receptor availability in Parkinson's disease in vivo," *Neurobiology of Aging*, vol. 33, no. 3, pp. 620.e1–620.e8, 2012.
- [142] E. M. Romero, B. Fernández, O. Sagredo et al., "Antinociceptive, behavioural and neuroendocrine effects of CP 55,940 in young rats," *Developmental Brain Research*, vol. 136, no. 2, pp. 85–92, 2002.
- [143] L. E. Long, R. Chesworth, X.-F. Huang, I. S. McGregor, J. C. Arnold, and T. Karl, "A behavioural comparison of acute and chronic 9-tetrahydrocannabinol and cannabidiol in C57BL/6JArc mice," *International Journal of Neuropsychopharmacology*, vol. 13, no. 7, pp. 861–876, 2010.
- [144] W. R. Prescott, L. H. Gold, and B. R. Martin, "Evidence for separate neuronal mechanisms for the discriminative stimulus and catalepsy induced by Δ^9 -THC in the rat," *Psychopharmacology*, vol. 107, no. 1, pp. 117–124, 1992.
- [145] J. N. Crawley, R. L. Corwin, J. K. Robinson, C. C. Felder, W. A. Devane, and J. Axelrod, "Anandamide, an endogenous ligand of the cannabinoid receptor, induces hypomotility and hypothermia in vivo in rodents," *Pharmacology, Biochemistry and Behavior*, vol. 46, no. 4, pp. 967–972, 1993.
- [146] J. Romero, R. de Miguel, E. García-Palomero, J. J. Fernández-Ruiz, and J. A. Ramos, "Time-course of the effects of anandamide, the putative endogenous cannabinoid receptor ligand, on extrapyramidal function," *Brain Research*, vol. 694, no. 1–2, pp. 223–232, 1995.
- [147] J. Romero, L. Garcia, M. Cebeira, D. Zadrozny, J. J. Fernández-Ruiz, and J. A. Ramos, "The endogenous cannabinoid receptor ligand, anandamide, inhibits the motor behavior: role of nigrostriatal dopaminergic neurons," *Life Sciences*, vol. 56, no. 23–24, pp. 2033–2040, 1995.
- [148] L. A. Anderson, J. J. Anderson, T. N. Chase, and J. R. Walters, "The cannabinoid agonists WIN 55,212-2 and CP 55,940 attenuate rotational behavior induced by a dopamine D1 but not a D2 agonist in rats with unilateral lesions of the nigrostriatal pathway," *Brain Research*, vol. 691, no. 1–2, pp. 106–114, 1995.
- [149] J. Fernández-Ruiz, I. Lastres-Becker, A. Cabranes, S. González, and J. A. Ramos, "Endocannabinoids and basal ganglia functionality," *Prostaglandins Leukotrienes and Essential Fatty Acids*, vol. 66, no. 2–3, pp. 257–267, 2002.
- [150] M. Herkenham, A. B. Lynn, M. Ross Johnson, L. S. Melvin, B. R. De Costa, and K. C. Rice, "Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study," *Journal of Neuroscience*, vol. 11, no. 2, pp. 563–583, 1991.
- [151] A. G. Hohmann and M. Herkenham, "Localization of cannabinoid CB1 receptor mRNA in neuronal subpopulations of rat striatum: a double-label in situ hybridization study," *Synapse*, vol. 37, no. 1, pp. 71–80, 2000.
- [152] J. Romero, I. Lastres-Becker, R. de Miguel, F. Berrendero, J. A. Ramos, and J. Fernández-Ruiz, "The endogenous cannabinoid system and the basal ganglia: biochemical, pharmacological, and therapeutic aspects," *Pharmacology and Therapeutics*, vol. 95, no. 2, pp. 137–152, 2002.
- [153] P. Gubellini, B. Picconi, M. Bari et al., "Experimental parkinsonism alters endocannabinoid degradation: implications for striatal glutamatergic transmission," *The Journal of Neuroscience*, vol. 22, no. 16, pp. 6900–6907, 2002.
- [154] Y. Gilgun-Sherki, E. Melamed, R. Mechoulam, and D. Offen, "The CB1 cannabinoid receptor agonist, HU-210, reduces levodopa-induced rotations in 6-hydroxydopamine-lesioned rats," *Pharmacology and Toxicology*, vol. 93, no. 2, pp. 66–70, 2003.
- [155] D. T. Malone and D. A. Taylor, "Modulation by fluoxetine of striatal dopamine release following Δ^9 -tetrahydrocannabinol: a microdialysis study in conscious rats," *British Journal of Pharmacology*, vol. 128, no. 1, pp. 21–26, 1999.
- [156] G. Tanda, F. E. Pontieri, and G. Di Chiara, "Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common μ 1 opioid receptor mechanism," *Science*, vol. 276, no. 5321, pp. 2048–2050, 1997.
- [157] R. G. Pertwee, A. Thomas, L. A. Stevenson et al., "The psychoactive plant cannabinoid, Δ^9 -tetrahydrocannabinol, is antagonized by Δ^8 - and Δ^9 -tetrahydrocannabivarin in mice in vivo," *British Journal of Pharmacology*, vol. 150, no. 5, pp. 586–594, 2007.
- [158] A. Richter and W. Löscher, "(+)-WIN 55,212-2, a novel cannabinoid receptor agonist, exerts antidystonic effects in mutant dystonic hamsters," *European Journal of Pharmacology*, vol. 264, no. 3, pp. 371–377, 1994.
- [159] Y. P. Maneuf, A. R. Crossman, and J. M. Brotchie, "The cannabinoid receptor agonist WIN 55,212-2 reduces D₂, but not D₁, dopamine receptor-mediated alleviation of akinesia

- in the reserpine-treated rat model of Parkinson's disease," *Experimental Neurology*, vol. 148, no. 1, pp. 265–270, 1997.
- [160] G. Segovia, F. Mora, A. R. Crossman, and J. M. Brotchie, "Effects of CB1 cannabinoid receptor modulating compounds on the hyperkinesia induced by high-dose levodopa in the reserpine-treated rat model of Parkinson's disease," *Movement Disorders*, vol. 18, no. 2, pp. 138–149, 2003.
- [161] M. G. Morgese, T. Cassano, V. Cuomo, and A. Giuffrida, "Anti-dyskinetic effects of cannabinoids in a rat model of Parkinson's disease: role of CB₁ and TRPV1 receptors," *Experimental Neurology*, vol. 208, no. 1, pp. 110–119, 2007.
- [162] M. G. Morgese, T. Cassano, S. Gaetani et al., "Neurochemical changes in the striatum of dyskinetic rats after administration of the cannabinoid agonist WIN55,212-2," *Neurochemistry International*, vol. 54, no. 1, pp. 56–64, 2009.
- [163] B. Ferrer, N. Asbrock, S. Kathuria, D. Piomelli, and A. Giuffrida, "Effects of levodopa on endocannabinoid levels in rat basal ganglia: implications for the treatment of levodopa-induced dyskinesias," *European Journal of Neuroscience*, vol. 18, no. 6, pp. 1607–1614, 2003.
- [164] R. González-Aparicio and R. Moratalla, "Oleoylethanolamide reduces L-DOPA-induced dyskinesia via TRPV1 receptor in a mouse model of Parkinson's disease," *Neurobiology of Disease*, vol. 62, pp. 416–425, 2014.
- [165] S. H. Fox, B. Henry, M. Hill, A. Crossman, and J. M. Brotchie, "Stimulation of Cannabinoid receptors reduces levodopa-induced dyskinesia in the MPTP-lesioned nonhuman primate model of Parkinson's disease," *Movement Disorders*, vol. 17, no. 6, pp. 1180–1187, 2002.
- [166] S. H. Fox, M. Kellett, A. P. Moore, A. R. Crossman, and J. M. Brotchie, "Randomised, double-blind, placebo-controlled trial to assess the potential of cannabinoid receptor stimulation in the treatment of dystonia," *Movement Disorders*, vol. 17, no. 1, pp. 145–149, 2002.
- [167] M. Solinas, Z. Justinova, S. R. Goldberg, and G. Tanda, "Anandamide administration alone and after inhibition of fatty acid amide hydrolase (FAAH) increases dopamine levels in the nucleus accumbens shell in rats," *Journal of Neurochemistry*, vol. 98, no. 2, pp. 408–419, 2006.
- [168] P. M. Zygmunt, J. Petersson, D. A. Andersson et al., "Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide," *Nature*, vol. 400, no. 6743, pp. 452–457, 1999.
- [169] D. Smart, M. J. Gunthorpe, J. C. Jerman et al., "The endogenous lipid anandamide is a full agonist at the human vanilloid receptor (hVR1)," *British Journal of Pharmacology*, vol. 129, no. 2, pp. 227–230, 2000.
- [170] V. Di Marzo, I. Lastres-Becker, T. Bisogno et al., "Hypolocomotor effects in rats of capsaicin and two long chain capsaicin homologues," *European Journal of Pharmacology*, vol. 420, no. 2-3, pp. 123–131, 2001.
- [171] S. Marinelli, V. Di Marzo, N. Berretta et al., "Presynaptic facilitation of glutamatergic synapses to dopaminergic neurons of the rat substantia nigra by endogenous stimulation of vanilloid receptors," *The Journal of Neuroscience*, vol. 23, no. 8, pp. 3136–3144, 2003.
- [172] P. B. Smith, D. R. Compton, S. P. Welch, R. K. Razdan, R. Mechoulam, and B. R. Martin, "The pharmacological activity of anandamide, a putative endogenous cannabinoid, in mice," *Journal of Pharmacology and Experimental Therapeutics*, vol. 270, no. 1, pp. 219–227, 1994.
- [173] E. Fride and R. Mechoulam, "Pharmacological activity of the cannabinoid receptor agonist, anandamide, a brain constituent," *European Journal of Pharmacology*, vol. 231, no. 2, pp. 313–314, 1993.
- [174] E. De Lago, J. Fernández-Ruiz, S. Ortega-Gutiérrez, A. Viso, M. L. López-Rodríguez, and J. A. Ramos, "UCM707, a potent and selective inhibitor of endocannabinoid uptake, potentiates hypokinetic and antinociceptive effects of anandamide," *European Journal of Pharmacology*, vol. 449, no. 1-2, pp. 99–103, 2002.
- [175] N. Ueda, R. A. Puffenbarger, S. Yamamoto, and D. G. Deutsch, "The fatty acid amide hydrolase (FAAH)," *Chemistry and Physics of Lipids*, vol. 108, no. 1-2, pp. 107–121, 2000.
- [176] M. Maccarrone, "Fatty acid amide hydrolase: a potential target for next generation therapeutics," *Current Pharmaceutical Design*, vol. 12, no. 6, pp. 759–772, 2006.
- [177] V. Di Marzo and M. Maccarrone, "FAAH and anandamide: is 2-AG really the odd one out?" *Trends in Pharmacological Sciences*, vol. 29, no. 5, pp. 229–233, 2008.
- [178] T. H. Johnston, P. Huot, S. H. Fox et al., "Fatty Acid Amide Hydrolase (FAAH) inhibition reduces L-3,4-dihydroxyphenylalanine-induced hyperactivity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned non-human primate model of Parkinson's disease," *Journal of Pharmacology and Experimental Therapeutics*, vol. 336, no. 2, pp. 423–430, 2011.
- [179] M. Celorrio, D. Fernández-Suárez, E. Rojo-Bustamante et al., "Fatty acid amide hydrolase inhibition for the symptomatic relief of Parkinson's disease," *Brain, Behavior, and Immunity*, vol. 57, pp. 94–105, 2016.
- [180] M. Hodaie, J. S. Neimat, and A. M. Lozano, "The dopaminergic nigrostriatal system and Parkinson's disease: molecular events in development, disease, and cell death, and new therapeutic strategies," *Neurosurgery*, vol. 60, no. 1, pp. 17–28, 2007.
- [181] A. Sayd, M. Antón, F. Alén et al., "Systemic administration of oleoylethanolamide protects from neuroinflammation and anhedonia induced by LPS in rats," *International Journal of Neuropsychopharmacology*, vol. 18, no. 6, pp. 1–14, 2015.
- [182] I. Lastres-Becker, F. Molina-Holgado, J. A. Ramos, R. Mechoulam, and J. Fernández-Ruiz, "Cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro: relevance to Parkinson's disease," *Neurobiology of Disease*, vol. 19, no. 1-2, pp. 96–107, 2005.
- [183] S. V. More, H. Kumar, I. S. Kim, S.-Y. Song, and D.-K. Choi, "Cellular and molecular mediators of neuroinflammation in the pathogenesis of Parkinson's disease," *Mediators of Inflammation*, vol. 2013, Article ID 952375, 12 pages, 2013.
- [184] M. García-Arencibia, L. Ferraro, S. Tanganelli, and J. Fernández-Ruiz, "Enhanced striatal glutamate release after the administration of rimonabant to 6-hydroxydopamine-lesioned rats," *Neuroscience Letters*, vol. 438, no. 1, pp. 10–13, 2008.
- [185] P. Huang, L.-Y. Liu-Chen, E. M. Unterwald, and A. Cowan, "Hyperlocomotion and paw tremors are two highly quantifiable signs of SR141716-precipitated withdrawal from delta9-tetrahydrocannabinol in C57BL/6 mice," *Neuroscience Letters*, vol. 465, no. 1, pp. 66–70, 2009.
- [186] S. González, C. Scorticati, M. García-Arencibia, R. de Miguel, J. A. Ramos, and J. Fernández-Ruiz, "Effects of rimonabant, a selective cannabinoid CB1 receptor antagonist, in a rat model of Parkinson's disease," *Brain Research*, vol. 1073-1074, no. 1, pp. 209–219, 2006.
- [187] E. Fernandez-Espejo, I. Caraballo, F. R. de Fonseca et al., "Cannabinoid CB1 antagonists possess antiparkinsonian efficacy only in rats with very severe nigral lesion in experimental parkinsonism," *Neurobiology of Disease*, vol. 18, no. 3, pp. 591–601, 2005.

- [188] F. El Banoua, I. Caraballo, J. A. Flores, B. Galan-Rodriguez, and E. Fernandez-Espejo, "Effects on turning of microinjections into basal ganglia of D1 and D2 dopamine receptors agonists and the cannabinoid CB1 antagonist SR141716A in a rat Parkinson's model," *Neurobiology of Disease*, vol. 16, no. 2, pp. 377–385, 2004.
- [189] X. Cao, L. Liang, J. R. Hadcock et al., "Blockade of cannabinoid type 1 receptors augments the antiparkinsonian action of levodopa without affecting dyskinesias in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated rhesus monkeys," *Journal of Pharmacology and Experimental Therapeutics*, vol. 323, no. 1, pp. 318–326, 2007.
- [190] S. M. Papa, "The cannabinoid system in Parkinson's disease: multiple targets to motor effects," *Experimental Neurology*, vol. 211, no. 2, pp. 334–338, 2008.
- [191] M. García-Arencibia, S. González, E. de Lago, J. A. Ramos, R. Mechoulam, and J. Fernández-Ruiz, "Evaluation of the neuroprotective effect of cannabinoids in a rat model of Parkinson's disease: importance of antioxidant and cannabinoid receptor-independent properties," *Brain Research*, vol. 1134, no. 1, pp. 162–170, 2007.
- [192] J. Fernández-Ruiz, M. Moreno-Martet, C. Rodríguez-Cueto et al., "Prospects for cannabinoid therapies in basal ganglia disorders," *British Journal of Pharmacology*, vol. 163, no. 7, pp. 1365–1378, 2011.
- [193] W. Gowers, *A Manual of Diseases of the Nervous System*, P. Blakiston's Son & Co, Philadelphia, Pa, USA, 1888.
- [194] K. R. Müller-Vahl, "Treatment of Tourette syndrome with cannabinoids," *Behavioural Neurology*, vol. 27, no. 1, pp. 119–124, 2013.
- [195] K. R. Müller-Vahl, U. Schneider, H. Prevedel et al., "Δ⁹-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial," *Journal of Clinical Psychiatry*, vol. 64, no. 4, pp. 459–465, 2003.
- [196] K. R. Müller-Vahl, U. Schneider, A. Koblenz et al., "Treatment of Tourette's syndrome with Δ⁹-tetrahydrocannabinol (THC): a randomized crossover trial," *Pharmacopsychiatry*, vol. 35, no. 2, pp. 57–61, 2002.
- [197] K. R. Müller-Vahl, H. Kolbe, U. Schneider, and H. M. Emrich, "Cannabis in movement disorders," *Forschende Komplementarmedizin*, vol. 6, no. 3, pp. 23–27, 1999.
- [198] K. R. Müller-Vahl, U. Schneider, and H. M. Emrich, "Nabilone increases choreatic movements in Huntington's disease," *Movement Disorders*, vol. 14, no. 6, pp. 1038–1040, 1999.
- [199] K. R. Müller-Vahl, H. Kolbe, U. Schneider, and H. M. Emrich, "Cannabinoids: possible role in patho-physiology and therapy of Gilles de la Tourette syndrome," *Acta Psychiatrica Scandinavica*, vol. 98, no. 6, pp. 502–506, 1998.
- [200] P. Consroe, R. Sandyk, and S. R. Snider, "Open label evaluation of cannabidiol in dystonic movement disorders," *International Journal of Neuroscience*, vol. 30, no. 4, pp. 277–282, 1986.
- [201] R. Sandyk, S. R. Snider, P. Consroe, and S. M. Elias, "Cannabidiol in dystonic movement disorders," *Psychiatry Research*, vol. 18, no. 3, p. 291, 1986.
- [202] K. Venderova, E. Ruzicka, V. Vorisek, and P. Visnovsky, "Survey on cannabis use in Parkinson's disease: subjective improvement of motor symptoms," *Movement Disorders*, vol. 19, no. 9, pp. 1102–1106, 2004.
- [203] I. Lotan, T. Treves, Y. Roditi, and R. Djaldetti, "Medical marijuana (cannabis) treatment for motor and non-motor symptoms in Parkinson's disease. An open-label observational study," *Movement Disorders*, vol. 28, no. 1, p. 448, 2013.
- [204] J. P. Frankel, A. Hughes, A. A. J. Lees, and G. M. Stern, "Marijuana for parkinsonian tremor," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 53, no. 5, p. 436, 1990.
- [205] C. B. Carroll, P. G. Bain, L. Teare, X. Liu, C. Joint, and C. Wroath, "Cannabis for dyskinesia in Parkinson disease: a randomized double-blind crossover study," *Neurology*, vol. 63, pp. 1245–1250, 2004.
- [206] S. R. Snider and P. Consroe, "Beneficial and adverse effects of cannabidiol in a Parkinson patient with sinemet-induced dystonic dyskinesia," *Neurology*, vol. 35, article 201, 1985.
- [207] K. A. Sieradzan, S. H. Fox, J. Dick, and J. M. Brotchie, "The effects of the cannabinoid receptor agonist nabilone on L-DOPA induced dyskinesia in patients with idiopathic Parkinson's disease," *Movement Disorders*, vol. 13, supplement 2, p. 29, 1998.
- [208] K. A. Sieradzan, S. H. Fox, M. Hill, J. P. R. Dick, A. R. Crossman, and J. M. Brotchie, "Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: A Pilot Study," *Neurology*, vol. 57, no. 11, pp. 2108–2111, 2001.
- [209] P. Consroe, "Brain cannabinoid systems as targets for the therapy of neurological disorders," *Neurobiology of Disease*, vol. 5, no. 6, pp. 534–551, 1998.
- [210] V. Mesnage, J. L. Houeto, A. M. Bonnet et al., "Neurokinin B, neurotensin, and cannabinoid receptor antagonists and Parkinson disease," *Clinical Neuropharmacology*, vol. 27, no. 3, pp. 108–110, 2004.
- [211] B. S. Koppel, J. C. M. Brust, T. Fife et al., "Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology," *Neurology*, vol. 82, no. 17, pp. 1556–1563, 2014.
- [212] A. Chatterjee, A. Almahrezi, M. Ware, and M. A. Fitzcharles, "A dramatic response to inhaled cannabis in a woman with central thalamic pain and dystonia," *Journal of Pain and Symptom Management*, vol. 24, no. 1, pp. 4–6, 2002.
- [213] C. D. Marsden, "Treatment of torsion dystonia," in *Disorders of Movement, Current Status of Modern Therapy*, A. Barbeau, Ed., vol. 8, pp. 81–104, Lippincott Williams & Wilkins, Philadelphia, Pa, USA, 1981.
- [214] M. C. Uribe Roca, F. Micheli, and R. Viotti, "Cannabis sativa and dystonia secondary to Wilson's disease," *Movement Disorders*, vol. 20, no. 1, pp. 113–115, 2005.
- [215] S. R. Snider and P. Consroe, "Treatment of Meige's syndrome with cannabidiol," *Neurology*, vol. 34, article 147, 1984.
- [216] R. Lorenz, "On the application of cannabis in paediatrics and epileptology," *Neuroendocrinology Letters*, vol. 25, no. 1-2, pp. 40–44, 2004.
- [217] A. Curtis, I. Mitchell, S. Patel, N. Ives, and H. Rickards, "A pilot study using nabilone for symptomatic treatment in Huntington's disease," *Movement Disorders*, vol. 24, no. 15, pp. 2254–2259, 2009.
- [218] M. J. Armstrong and J. M. Miyasaki, "Evidence-based guideline: pharmacologic treatment of chorea in Huntington disease: report of the guideline development subcommittee of the American Academy of Neurology," *Neurology*, vol. 79, no. 6, pp. 597–603, 2012.
- [219] R. Sandyk, P. Consroe, L. Stern, S. R. Snider, and D. Bliklen, "Preliminary trial of cannabidiol in Huntington's disease," in *Marijuana: An International Research Report*, G. Chesher, P. Consroe, and R. Musty, Eds., Australian Government Publishing Service, Canberra, Australia, 1988.

- [220] P. Consroe, J. Laguna, J. Allender et al., "Controlled clinical trial of cannabidiol in Huntington's disease," *Pharmacology, Biochemistry and Behavior*, vol. 40, no. 3, pp. 701–708, 1991.
- [221] N. M. Kogan and R. Mechoulam, "Cannabinoids in health and disease," *Dialogues in Clinical Neuroscience*, vol. 9, no. 4, pp. 413–430, 2007.
- [222] R. Sandyk and G. Awerbuch, "Marijuana and tourette's syndrome," *Journal of Clinical Psychopharmacology*, vol. 8, no. 6, pp. 444–445, 1988.
- [223] M. Hemming and P. M. Yellowlees, "Effective treatment of Tourette's syndrome with marijuana," *Journal of Psychopharmacology*, vol. 7, no. 4, pp. 389–391, 1993.
- [224] A. Hasan, A. Rothenberger, A. Münchau, T. Wobrock, P. Falkai, and V. Roessner, "Oral Δ^9 -tetrahydrocannabinol improved refractory Gilles de la Tourette syndrome in an adolescent by increasing intracortical inhibition: a case report," *Journal of Clinical Psychopharmacology*, vol. 30, no. 2, pp. 190–192, 2010.
- [225] A. Brunnauer, F. M. Segmiller, T. Volkamer, G. Laux, N. Müller, and S. Dehning, "Cannabinoids improve driving ability in a Tourette's patient," *Psychiatry Research*, vol. 190, no. 2-3, p. 382, 2011.
- [226] G. Berding, K. Müller-Vahl, U. Schneider et al., "[123 I]AM281 single-photon emission computed tomography imaging of central cannabinoid CB1 receptors before and after Δ^9 -tetrahydrocannabinol therapy and whole-body scanning for assessment of radiation dose in Tourette patients," *Biological Psychiatry*, vol. 55, no. 9, pp. 904–915, 2004.
- [227] J. Ševčík and K. Mašek, "Potential role of cannabinoids in Parkinson's disease," *Drugs and Aging*, vol. 16, no. 6, pp. 391–395, 2000.
- [228] H. Pan, P. Mukhopadhyay, M. Rajesh et al., "Cannabidiol attenuates cisplatin-Induced nephrotoxicity by decreasing oxidative/nitrosative stress, inflammation, and cell death," *Journal of Pharmacology and Experimental Therapeutics*, vol. 328, no. 3, pp. 708–714, 2009.
- [229] M. S. Hernandez, C. C. Café-Mendes, and L. R. G. Britto, "NADPH oxidase and the degeneration of dopaminergic neurons in Parkinsonian mice," *Oxidative Medicine and Cellular Longevity*, vol. 2013, Article ID 157857, 13 pages, 2013.
- [230] E. Hebert-Chatelain, L. Reguero, N. Puente et al., "Cannabinoid control of brain bioenergetics: exploring the subcellular localization of the CB1 receptor," *Molecular Metabolism*, vol. 3, no. 4, pp. 495–504, 2014.
- [231] S. Yamaori, J. Ebisawa, Y. Okushima, I. Yamamoto, and K. Watanabe, "Potent inhibition of human cytochrome P450 3A isoforms by cannabidiol: role of phenolic hydroxyl groups in the resorcinol moiety," *Life Sciences*, vol. 88, no. 15-16, pp. 730–736, 2011.
- [232] A. J. Hampson, M. Grimaldi, J. Axelrod, and D. Wink, "Cannabidiol and (-)- Δ^9 -tetrahydrocannabinol are neuroprotective antioxidants," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 14, pp. 8268–8273, 1998.
- [233] G. Bénard, F. Massa, N. Puente et al., "Mitochondrial CB1 receptors regulate neuronal energy metabolism," *Nature Neuroscience*, vol. 15, no. 4, pp. 558–564, 2012.
- [234] S. Amor, F. Puentes, D. Baker, and P. Van Der Valk, "Inflammation in neurodegenerative diseases," *Immunology*, vol. 129, no. 2, pp. 154–169, 2010.
- [235] S. Amor, L. A. N. Peferoen, D. Y. S. Vogel et al., "Inflammation in neurodegenerative diseases—an update," *Immunology*, vol. 142, no. 2, pp. 151–166, 2014.
- [236] L. F. Clark and T. Kodadek, "The immune system and neuroinflammation as potential sources of blood-based biomarkers for Alzheimer's disease, Parkinson's disease, and huntington's disease," *ACS Chemical Neuroscience*, vol. 7, no. 5, pp. 520–527, 2016.
- [237] M. A. Mena and J. García De Yébenes, "Glial cells as players in parkinsonism: the 'good,' the 'bad,' and the 'mysterious' glia," *Neuroscientist*, vol. 14, no. 6, pp. 544–560, 2008.
- [238] P. L. McGeer and E. G. McGeer, "Glial reactions in Parkinson's disease," *Movement Disorders*, vol. 23, no. 4, pp. 474–483, 2008.
- [239] N. Stella, "Cannabinoid and cannabinoid-like receptors in microglia, astrocytes, and astrocytomas," *Glia*, vol. 58, no. 9, pp. 1017–1030, 2010.
- [240] A. Klegeris, C. J. Bissonnette, and P. L. McGeer, "Reduction of human monocytic cell neurotoxicity and cytokine secretion by ligands of the cannabinoid-type CB2 receptor," *British Journal of Pharmacology*, vol. 139, no. 4, pp. 775–786, 2003.
- [241] G. Esposito, C. Scuderi, C. Savani et al., "Cannabidiol in vivo blunts β -amyloid induced neuroinflammation by suppressing IL-1 β and iNOS expression," *British Journal of Pharmacology*, vol. 151, no. 8, pp. 1272–1279, 2007.
- [242] B. Watzl, P. Scuderi, and R. R. Watson, "Influence of marijuana components (THC and CBD) on human mononuclear cell cytokine secretion in vitro," *Advances in Experimental Medicine and Biology*, vol. 288, pp. 63–70, 1991.
- [243] M. D. Srivastava, B. I. S. Srivastava, and B. Brouhard, " Δ^9 Tetrahydrocannabinol and cannabidiol alter cytokine production by human immune cells," *Immunopharmacology*, vol. 40, no. 3, pp. 179–185, 1998.
- [244] A. M. Malfait, R. Gallily, P. F. Sumariwalla et al., "The nonpsychoactive cannabis constituent cannabidiol is an oral antiarthritic therapeutic in murine collagen-induced arthritis," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 17, pp. 9561–9566, 2000.
- [245] R. Mechoulam, L. A. Parker, and R. Gallily, "Cannabidiol: an overview of some pharmacological aspects," *Journal of Clinical Pharmacology*, vol. 42, no. 11, pp. 11S–19S, 2002.
- [246] R. Mechoulam, M. Peters, E. Murillo-Rodriguez, and L. O. Hanuš, "Cannabidiol—recent advances," *Chemistry and Biodiversity*, vol. 4, no. 8, pp. 1678–1692, 2007.
- [247] B. Costa, M. Colleoni, S. Conti et al., "Oral anti-inflammatory activity of cannabidiol, a non-psychoactive constituent of cannabis, in acute carrageenan-induced inflammation in the rat paw," *Naunyn-Schmiedeberg's Archives of Pharmacology*, vol. 369, no. 3, pp. 294–299, 2004.
- [248] B. Costa, A. E. Trovato, F. Comelli, G. Giagnoni, and M. Colleoni, "The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain," *European Journal of Pharmacology*, vol. 556, no. 1–3, pp. 75–83, 2007.
- [249] F. Assaf, M. Fishbein, M. Gafni, O. Keren, and Y. Sarne, "Pre- and post-conditioning treatment with an ultra-low dose of Δ^9 -tetrahydrocannabinol (THC) protects against pentylenetetrazole (PTZ)-induced cognitive damage," *Behavioural Brain Research*, vol. 220, no. 1, pp. 194–201, 2011.
- [250] P. E. Szmítka and S. Verma, "Does cannabis hold the key to treating cardiometabolic disease?" *Nature Clinical Practice Cardiovascular Medicine*, vol. 3, no. 3, pp. 116–117, 2006.
- [251] M. Fishbein-Kaminietsky, M. Gafni, and Y. Sarne, "Ultralow doses of cannabinoid drugs protect the mouse brain from inflammation-induced cognitive damage," *Journal of Neuroscience Research*, vol. 92, no. 12, pp. 1669–1677, 2014.

- [252] O. Sagredo, M. García-Arencibia, E. de Lago, S. Finetti, A. Decio, and J. Fernández-Ruiz, "Cannabinoids and neuroprotection in basal ganglia disorders," *Molecular Neurobiology*, vol. 36, no. 1, pp. 82–91, 2007.
- [253] D. A. Price, A. A. Martinez, A. Seillier et al., "WIN55,212-2, a cannabinoid receptor agonist, protects against nigrostriatal cell loss in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease," *European Journal of Neuroscience*, vol. 29, no. 11, pp. 2177–2186, 2009.
- [254] J. Martínez-Orgado, D. Fernández-López, I. Lizasoain, and J. Romero, "The seek of neuroprotection: introducing cannabinoids," *Recent Patents on CNS Drug Discovery*, vol. 2, no. 2, pp. 131–139, 2007.
- [255] J. Romero and J. Martínez-Orgado, "Cannabinoids and neurodegenerative diseases," *CNS and Neurological Disorders—Drug Targets*, vol. 8, no. 6, pp. 440–450, 2009.
- [256] M. F. Beal, "Excitotoxicity and nitric oxide in Parkinson's disease pathogenesis," *Annals of Neurology*, vol. 44, no. 3, pp. S110–S114, 1998.
- [257] S. Valdeolivas, V. Satta, R. G. Pertwee, J. Fernández-Ruiz, and O. Sagredo, "Sativex-like combination of phytocannabinoids is neuroprotective in malonate-lesioned rats, an inflammatory model of Huntington's disease: role of CB1 and CB2 receptors," *ACS Chemical Neuroscience*, vol. 3, no. 5, pp. 400–406, 2012.
- [258] M. Zeissler, C. Hanemann, J. Zajicek, and C. Carroll, "FAAH inhibition is protective in a cell culture model of Parkinson's disease," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 83, supplement 2, p. A15, 2012.
- [259] M. Sophie and B. Ford, "Management of pain in Parkinson's disease," *CNS Drugs*, vol. 26, no. 11, pp. 937–948, 2012.
- [260] E. G. Silva, M. A. Viana, and E. M. Quagliato, "Diagnostic of parkinsonian syndrome in a Brazilian movement disorders clinic," *Revista Neurociências*, vol. 13, no. 4, pp. 173–177, 2005.
- [261] M. Tinazzi, C. Del Vesco, E. Fincati et al., "Pain and motor complications in Parkinson's disease," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 77, no. 7, pp. 822–825, 2006.
- [262] J. I. Sage, "Pain in Parkinson's disease," *Current Treatment Options in Neurology*, vol. 6, no. 3, pp. 191–200, 2004.
- [263] R. H. Dworkin, E. M. Nagasako, B. S. Galer, R. D. Hetzel, and J. T. Farrar, "Assessment of pain and pain-related quality of life in clinical trials," in *Handbook of Pain Assessment*, D. C. Turk and R. Melzack, Eds., pp. 519–548, Guilford, New York, NY, USA, 2nd edition, 2001.
- [264] R. H. Dworkin, M. Backonja, M. C. Rowbotham et al., "Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations," *Archives of Neurology*, vol. 60, no. 11, pp. 1524–1534, 2003.
- [265] R. H. Dworkin, A. E. Corbin, J. P. Young Jr. et al., "Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial," *Neurology*, vol. 60, no. 8, pp. 1274–1283, 2003.
- [266] L. Greenbaum, I. Tegeder, Y. Barhum, E. Melamed, Y. Roditi, and R. Djaldetti, "Contribution of genetic variants to pain susceptibility in Parkinson disease," *European Journal of Pain*, vol. 16, no. 9, pp. 1243–1250, 2012.
- [267] A. Calignano, G. La Rana, A. Giuffrida, and D. Piomelli, "Control of pain initiation by endogenous cannabinoids," *Nature*, vol. 394, no. 6690, pp. 277–281, 1998.
- [268] R. J. Ellis, W. Toperoff, F. Vaida et al., "Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial," *Neuropsychopharmacology*, vol. 34, no. 3, pp. 672–680, 2009.
- [269] B. Wilsey, T. Marcotte, A. Tsodikov et al., "A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain," *Journal of Pain*, vol. 9, no. 6, pp. 506–521, 2008.
- [270] D. I. Abrams, C. A. Jay, S. B. Shade et al., "Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial," *Neurology*, vol. 68, no. 7, pp. 515–521, 2007.
- [271] J. S. Berman, C. Symonds, and R. Birch, "Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial," *Pain*, vol. 112, no. 3, pp. 299–306, 2004.
- [272] K. B. Svendsen, T. S. Jensen, and F. W. Bach, "Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial," *British Medical Journal*, vol. 329, no. 7460, pp. 253–257, 2004.
- [273] D. J. Rog, T. J. Nurmikko, T. Friede, and C. A. Young, "Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis," *Neurology*, vol. 65, no. 6, pp. 812–819, 2005.
- [274] T. J. Nurmikko, M. G. Serpell, B. Hoggart, P. J. Toomey, B. J. Morlion, and D. Haines, "Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial," *Pain*, vol. 133, no. 1–3, pp. 210–220, 2007.
- [275] K. P. Hill, "Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review," *The Journal of the American Medical Association*, vol. 313, no. 24, pp. 2474–2483, 2015.
- [276] M. E. Lynch and F. Campbell, "Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials," *British Journal of Clinical Pharmacology*, vol. 72, no. 5, pp. 735–744, 2011.
- [277] M. I. Martín Fontelles and C. Goicoechea García, "Role of cannabinoids in the management of neuropathic pain," *CNS Drugs*, vol. 22, no. 8, pp. 645–653, 2008.
- [278] M. Iskedjian, B. Bereza, A. Gordon, C. Piwko, and T. R. Einarson, "Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain," *Current Medical Research and Opinion*, vol. 23, no. 1, pp. 17–24, 2007.
- [279] S. Corey, "Recent developments in the therapeutic potential of cannabinoids," *Puerto Rico Health Sciences Journal*, vol. 24, no. 1, pp. 19–26, 2005.
- [280] P. F. Smith, "Cannabinoids in the treatment of pain and spasticity in multiple sclerosis," *Current Opinion in Investigational Drugs*, vol. 3, no. 6, pp. 859–864, 2002.
- [281] F. A. Campbell, M. R. Tramèr, D. Carroll, D. J. M. Reynolds, R. A. Moore, and H. J. McQuay, "Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review," *British Medical Journal*, vol. 323, no. 7303, pp. 13–16, 2001.
- [282] W. J. G. Hoogendijk, I. E. C. Sommer, G. Tissingh, D. J. H. Deeg, and E. C. Wolters, "Depression in Parkinson's disease: the impact of symptom overlap on prevalence," *Psychosomatics*, vol. 39, no. 5, pp. 416–421, 1998.
- [283] M. Yamamoto, "Depression in Parkinson's disease: its prevalence, diagnosis, and neurochemical background," *Journal of Neurology*, vol. 248, no. 3, pp. III5–II, 2001.
- [284] J. S. A. M. Reijnders, U. Ehrt, W. E. J. Weber, D. Aarsland, and A. F. G. Leentjens, "A systematic review of prevalence studies of depression in Parkinson's disease," *Movement Disorders*, vol. 23, no. 2, pp. 183–189, 2008.

- [285] A. Schrag, A. Hovris, D. Morley, N. Quinn, and M. Jahanshahi, "Caregiver-burden in parkinson's disease is closely associated with psychiatric symptoms, falls, and disability," *Parkinsonism & Related Disorders*, vol. 12, no. 1, pp. 35–41, 2006.
- [286] A. Schrag, "Quality of life and depression in Parkinson's disease," *Journal of the Neurological Sciences*, vol. 248, no. 1-2, pp. 151–157, 2006.
- [287] H. Reichmann, C. Schneider, and M. Löhle, "Non-motor features of Parkinson's disease: depression and dementia," *Parkinsonism and Related Disorders*, vol. 15, no. 3, pp. S87–S92, 2009.
- [288] B. B. Gorzalka and M. N. Hill, "Putative role of endocannabinoid signaling in the etiology of depression and actions of antidepressants," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 35, no. 7, pp. 1575–1585, 2011.
- [289] M. Navarro, E. Hernández, R. M. Muñoz et al., "Acute administration of the CB1 cannabinoid receptor antagonist SR 141716A induces anxiety-like responses in the rat," *NeuroReport*, vol. 8, no. 2, pp. 491–496, 1997.
- [290] F. A. Moreira and B. Lutz, "The endocannabinoid system: emotion, learning and addiction," *Addiction Biology*, vol. 13, no. 2, pp. 196–212, 2008.
- [291] F. A. Moreira and J. A. S. Crippa, "The psychiatric side-effects of rimonabant," *Revista Brasileira de Psiquiatria*, vol. 31, no. 2, pp. 145–153, 2009.
- [292] F. J. Barrero, I. Ampuero, B. Morales et al., "Depression in Parkinson's disease is related to a genetic polymorphism of the cannabinoid receptor gene (CNRI)," *The Pharmacogenomics Journal*, vol. 5, no. 2, pp. 135–141, 2005.
- [293] F. R. Bambico, P. R. Hattan, J. P. Garant, and G. Gobbi, "Effect of delta-9-tetrahydrocannabinol on behavioral despair and on pre- and postsynaptic serotonergic transmission," *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, vol. 38, no. 1, pp. 88–96, 2012.
- [294] G. Gobbi, F. R. Bambico, R. Mangieri et al., "Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 51, pp. 18620–18625, 2005.
- [295] T. F. Denson and M. Earleywine, "Decreased depression in marijuana users," *Addictive Behaviors*, vol. 31, no. 4, pp. 738–742, 2006.
- [296] L. Degenhardt, W. Hall, and M. Lynskey, "Exploring the association between cannabis use and depression," *Addiction*, vol. 98, no. 11, pp. 1493–1504, 2003.
- [297] B. Porter, R. MacFarlane, and R. Walker, "The frequency and nature of sleep disorders in a community-based population of patients with Parkinson's disease," *European Journal of Neurology*, vol. 15, no. 1, pp. 46–50, 2008.
- [298] A. Videnovic and D. Golombek, "Circadian and sleep disorders in Parkinson's disease," *Experimental Neurology*, vol. 243, pp. 45–56, 2013.
- [299] L. M. Trotti and D. L. Bliwise, "Treatment of the sleep disorders associated with Parkinson's disease," *Neurotherapeutics*, vol. 11, no. 1, pp. 68–77, 2014.
- [300] M. Stacy, "Sleep disorders in Parkinson's disease: epidemiology and management," *Drugs and Aging*, vol. 19, no. 10, pp. 733–739, 2002.
- [301] E. B. Russo, G. W. Guy, and P. J. Robson, "Cannabis, pain, and sleep: lessons from therapeutic clinical trials of sativex, a cannabis-based medicine," *Chemistry & Biodiversity*, vol. 4, no. 8, pp. 1729–1743, 2007.

Cannabinoids and Epilepsy

Evan C. Rosenberg¹ · Richard W. Tsien¹ · Benjamin J. Whalley² · Orrin Devinsky³

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Abstract Cannabis has been used for centuries to treat seizures. Recent anecdotal reports, accumulating animal model data, and mechanistic insights have raised interest in cannabis-based antiepileptic therapies. In this study, we review current understanding of the endocannabinoid system, characterize the pro- and anticonvulsive effects of cannabinoids [e.g., Δ^9 -tetrahydrocannabinol and cannabidiol (CBD)], and highlight scientific evidence from pre-clinical and clinical trials of cannabinoids in epilepsy. These studies suggest that CBD avoids the psychoactive effects of the endocannabinoid system to provide a well-tolerated, promising therapeutic for the treatment of seizures, while whole-plant cannabis can both contribute to and reduce seizures. Finally, we discuss results from a new multicenter, open-label study using CBD in a population with treatment-resistant epilepsy. In all, we seek to evaluate our current understanding of cannabinoids in epilepsy and guide future basic science and clinical studies.

Keywords Epilepsy · seizures · cannabinoids · cannabidiol · THC · cannabis

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✉ Orrin Devinsky
od4@nyu.edu

¹ Department of Neuroscience and Physiology, Neuroscience Institute, NYU Langone Medical Center, New York, NY 10016, USA

² School of Pharmacy, The University of Reading, Whiteknights, Reading RG6 6AP, UK

³ Department of Neurology, Comprehensive Epilepsy Center, New York University School of Medicine, New York, NY 10016, UK

Introduction

Epilepsy affects 2.9 million people in the USA and 65 million people worldwide (cdc.gov/epilepsy). One in 26 people in the USA will develop epilepsy in their lifetime [1]. Characterized by recurrent seizures, epilepsy encompasses multiple disorders caused by varied etiologies, including genetic syndromes, stroke, infection, and traumatic brain injury. Many patients with epilepsy also have sensorimotor, cognitive, psychological, psychiatric, and social impairments, as well as impaired quality of life and an increased risk of premature death [1]. While epilepsy can affect patients of all ages, it most commonly affects children, the elderly, and individuals with low socioeconomic status. The estimated direct and indirect annual cost of epilepsy in the U.S. is \$15.5 billion (cdc.gov/epilepsy).

While many drugs can limit seizures, no drug can prevent the underlying cause of epilepsy or the development of epilepsy (epileptogenesis) in patients who are at risk (e.g., after head trauma). A third of patients remain pharmacoresistant, failing to achieve sustained seizure freedom after 2 or more adequately chosen, tolerated, and appropriately used antiepileptic drugs (AEDs; more accurately termed antiseizure drugs) [2–4]. Patients resistant to multiple AEDs have an increased risk for sudden unexpected death in epilepsy and other forms of epilepsy-related mortality [5, 6], as well as impairments in psychosocial, behavioral, and cognitive functions [3, 7–9]. For many patients, epilepsy is a progressive disorder associated with ongoing loss of brain tissue and function. Finally, multidrug combinations and high dosages cause more severe side effects, a particular problem in patients with treatment-resistant epilepsies. Assessing the side effects of AEDs is especially challenging in patients on long-term AEDs as any ‘baseline’ may be many years past and even intelligent adults, parents, and physicians may fail to appreciate chronic adverse

effects. The available AEDs fail to meet the clinical needs for both efficacy and safety [10], indicating a dire need for novel therapeutics that are targeted, disease-, and age-specific.

Recently, mounting anecdotal reports and media coverage have sparked intense interest among parents, patients, and the scientific community regarding the potential of medical cannabis to treat seizures. A potential alternative or supplement to current AEDs, the cannabis plant includes >100 diverse phytocannabinoids that, in part, target an endogenous endocannabinoid signaling network, as well as other networks. Two major phytocannabinoids derived from cannabis are psychoactive Δ^9 -tetrahydrocannabinol (THC) and nonpsychoactive cannabidiol (CBD). Both Δ^9 -THC and CBD can prevent seizures and reduce mortality in animal models of seizure with low toxicity and high tolerability [11]. However, a systematic analysis from the American Academy of Neurology and a Cochrane Database review both concluded that medical cannabis is of “unknown efficacy” to treat epilepsy [12, 13]. In this review, we examine the history of cannabinoids in epilepsy, discuss the effectiveness of preclinical seizure model studies with cannabinoids, and review recent clinical data, including a multicenter clinical trial of CBD for patients with treatment-resistant epilepsy.

History of Cannabis in Epilepsy

Cannabis has been used for millennia for medical, recreational, and manufacturing purposes. Around 2900 BCE, the Chinese Emperor Fu Hsi characterized cannabis as having sacred yin (weak, passive forces) and yang (strong, active forces) features, suggesting that it could restore homeostasis to an unbalanced body. Physicians in ancient India, Egypt, Persia, Rome, Arabia, and Greece used cannabis for spiritual and medicinal purposes, including menstrual fatigue, gout, rheumatism, malaria, beriberi, constipation, pain, and absentmindedness [14]. Early documented uses of cannabis to treat seizures include a Sumerian text from 2900 BCE and an Arabian document from the twelfth century [15, 16].

The 1854, the US Dispensatory listed cannabis to treat neuralgia, depression, pain, muscle spasms, insomnia, tetanus, chorea, insanity, and other disorders [17]. Cannabis was valued for its analgesic, anti-inflammatory, appetite-stimulating, and antibiotic properties. In the mid-1800s, the British surgeon William O’Shaughnessy reported cannabis therapy for the treatment of epilepsy, recounting an “alleviation of pain in most, a remarkable increase of appetite in all, unequivocal aphrodisia, and great mental cheerfulness” [14, 18]. Two of England’s most prominent mid-to-late nineteenth-century neurologists, J.R. Reynolds and W. Gowers, also noted the benefits of cannabis in epilepsy [19]. Gowers reported a man who previously failed bromides whose seizures were

controlled on 9.8 g of *Cannabis indica*, dosed 3 times daily for up to 6 months [20].

Cannabis was first regulated in the USA with the 1906 “Pure Food and Drug Act”. The follow-up 1937 Marijuana Tax Act was opposed by the American Medical Association, which considered the more severe restrictions an infringement on physician’s freedom to treat patients [17]. In 1970, the US Comprehensive Drug Abuse Prevention and Control Act categorized marijuana as a Schedule I drug with high potential for abuse and no accepted medicinal use. Legislation has been introduced to the US Senate to change marijuana to a Schedule II drug.

Over the last 50 years, the main chemical constituents of cannabis have been isolated and synthesized. Δ^9 -THC was isolated in 1964 and synthesized in 1971 [21, 22]. CBD was isolated in 1940 and synthesized in 1963 [23, 24]. The cannabinoid type 1 (CB₁R) and type 2 (CB₂R) receptors, which bind Δ^9 -THC, were cloned in the 1990s [25, 26], supporting an endogenous system for this principal cannabinoid’s pharmacological activity.

The Endocannabinoid System

The discovery of the endocannabinoid system in the early 1990s revealed the neuronal mechanisms that underlie the psychoactive effects of Δ^9 -THC in cannabis. Initial studies demonstrated that brief postsynaptic depolarization reduced neurotransmitter release from excitatory terminals onto Purkinje cells in the cerebellum and inhibitory terminals onto pyramidal neurons in the hippocampus [27, 28]. This phenomenon was termed “depolarization-induced suppression of excitation/inhibition” (DSE and DSI, respectively). Postsynaptic depolarization was postulated to trigger the release of an undiscovered substance that transiently limited presynaptic neurotransmitter release. Along with the discovery of nitric oxide (NO), this paradigm-shifting view suggested the concept of retrograde signaling in contrast to a primarily anterograde view of synaptic signaling. Application of a CB₁R agonist (or antagonist) enhanced (or prevented) DSE and DSI, suggesting that it was mediated by an endogenous cannabinoid ligand [29–31]. These endocannabinoids were identified as the hydrophobic ligands *N*-arachidonoyl ethanolamide (anandamide) [32] and 2-arachidonoyl glycerol (2-AG) [33, 34].

Anandamide and 2-AG are synthesized from postsynaptic membrane phospholipid precursors and released in an activity-dependent, “on-demand” manner, unlike traditional vesicular neurotransmitters (Fig. 1). Depolarization of the postsynaptic cell or direct activation of metabotropic glutamate receptors increases levels of intracellular calcium, which trigger second messenger cascades that promote endocannabinoid synthesis [35–39]. Anandamide is synthesized via

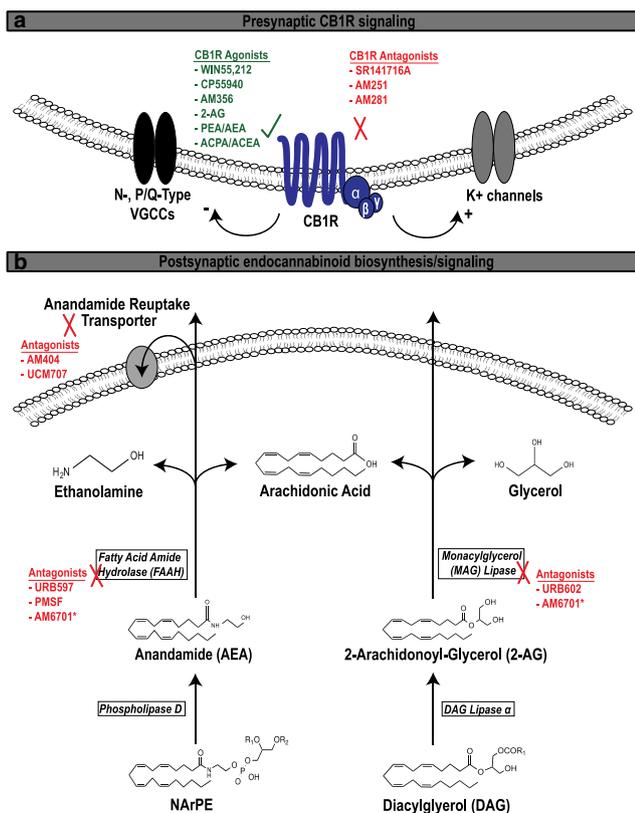


Fig. 1 Biosynthesis, degradation, and signaling of endocannabinoids. (A) Presynaptic cannabinoid type 1 receptor (CB₁R) signaling. (B) Postsynaptic endocannabinoid biosynthesis/signaling. NArPE = *N*-arachidonoyl phosphatidylethanolamine; DAG = 1-acyl, 2-arachidonoyl diacylglycerol; VGCC = voltage-gated calcium channels; PEA = palmitoylethanolamide; ACPA = arachidonylcyclopropylamide; ACEA = arachidonyl-2'-chloroethylamide; PMSF = phenylmethylsulfonyl fluoride

phospholipase D-mediated hydrolysis of *N*-arachidonoyl-phosphatidylethanolamine, and degraded by the fatty acid amide hydrolase (FAAH) into arachidonic acid and ethanolamine [40–43]. 2-AG is synthesized via diacylglycerol (DAG) lipase (DAGL) α -mediated hydrolysis of DAG, and degraded by FAAH into arachidonic acid and glycerol, or by monoacylglycerol lipase [41–44]. Chronic hyperexcitability leads to dynamic changes in the endocannabinoid pathway (see “The Endocannabinoid System: CB₁Rs”). Thus, the enzymes that regulate metabolism and cannabinoid receptors represent attractive targets to treat several neurological disorders [45]. Accordingly, the selective CB₁R blocker rimonabant was approved in >50 countries as an anorectic to treat obesity [46], and showed promise in helping smokers quit tobacco use [47], but its use was suspended when postmarketing surveillance revealed high rates of depression and suicidal ideation.

Produced in an activity-dependent manner, endocannabinoids travel to the presynaptic cell and bind to CB₁Rs. CB₁Rs are G protein-coupled receptors linked to pertussis-sensitive Gi/o α subunits. Activation of the α subunit triggers dissociation of the $\beta\gamma$ complex, which reduces adenylate cyclase production

of cyclic adenosine monophosphate [48], inhibits N- and P/Q-type voltage-gated calcium channels [31, 49–52], stimulates A-type potassium channels [53–56], activates G protein-coupled inwardly-rectifying potassium channels [57–59], and inhibits the vesicular release machinery [60]. These multiple mechanisms reduce presynaptic cell excitability and Ca²⁺, strongly diminishing presynaptic neurotransmitter release. CB₁Rs can also regulate the presynaptic release of multiple neuromodulators such as acetylcholine, dopamine, and norepinephrine [61]. Finally, endocannabinoid signaling may modulate regional-specific long-term synaptic plasticity, including long-term potentiation and long-term depression (for a review, see [62, 63]).

CB₁Rs are distributed primarily in axon terminals in the neocortex (especially cingulate, frontal, and parietal regions), hippocampus, amygdala, basal ganglia, thalamus, hypothalamus, nucleus accumbens, substantia nigra, ventral tegmental area, cerebellum, and brainstem [39]. CB₁Rs are most densely expressed at cortical and hippocampal presynaptic γ -aminobutyric acid (GABA)ergic presynaptic boutons, especially cholecystokinin-positive (CCK+) and parvalbumin-negative GABAergic interneurons [64–66]. Glutamatergic axon terminals in cortical and subcortical neurons contain fewer presynaptic CB₁ receptors than GABAergic terminals [65, 67–71].

Phytocannabinoids: Classification and Function

The cannabis plant consists contains >100 C₂₁ terpenophenolic compounds, known collectively as phytocannabinoids [72]. Most of these lipophilic cannabinoids are closely related and differ only by a single chemical functional group. Cannabinoids fall into 10 main groups, with constituents representing degradation products, precursors, or byproducts (Fig. 2, adapted from [73]). Two of the most abundant constituents are Δ 9-THC and CBD, the ratios of which vary by cannabis strain. *Cannabis sativa* contains a higher ratio of Δ 9-THC to CBD, producing more stimulating, psychotropic effects. *Cannabis indica* strains contains a higher ratio of CBD: Δ 9-THC and are typically more sedating [11, 73].

Δ 9-THC

Δ 9-THC is a partial agonist at central nervous system (CNS) CB₁Rs and CB₂Rs in the immune system. Most behavioral, cognitive, and psychotropic effects of cannabis result from the effects of Δ 9-THC at brain CB₁Rs. The subjective “high” produced by cannabis can be blocked by pretreatment with the CB₁R antagonist rimonabant [74]. Δ 9-THC impairs short-term working memory in several rodent models, which can be reversed by preapplication of a CB₁R antagonist [75–78]. Inhibition of long-term potentiation at hippocampal CA3 Schaffer Collateral/CA1 synapses may underlie this

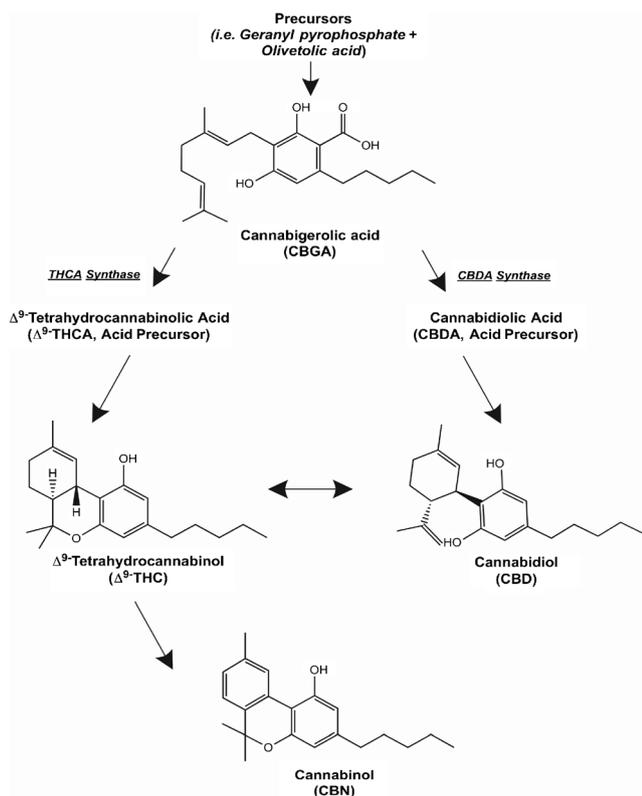


Fig. 2 Biosynthesis of phytocannabinoids [73]

effect on memory [35]. Δ⁹-THC or CB₁R agonists can increase or decrease food intake in different species [79]. Δ⁹-THC also regulates neuronal excitability during seizures (see “Preclinical Evidence”). Thus, Δ⁹-THC acts through the endocannabinoid system to regulate mood, learning and memory, neuronal excitability, and energy balance. Δ⁹-THC exerts potent anti-inflammatory functions via CB₁Rs and CB₂Rs on microglia, the primary immune cells in the CNS. Δ⁹-THC or CB₁R agonists limit neurotoxicity in *in vitro* and *in vivo* assays, including chemotoxic [80–83], low Mg²⁺ [84], and ischemic [85, 86] models. Δ⁹-THC has antioxidant effects in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid- and *N*-methyl-D-aspartate-mediated cytotoxicity models via a CB₁R-independent mechanism [87]. Cannabinoids reduce neuronal and glial release of the proinflammatory cytokines tumor necrosis factor-α, NO, interleukin (IL)-1 and IL-6 [88–93], and increase release of anti-inflammatory cytokines IL-4, IL-10, and IL-1 receptor antagonist (IL-1a) [94, 95] via CB₁R- and CB₂R-dependent mechanisms in neurons and glia [94, 95] (reviewed in [96]). Δ⁹-THC also transiently activates and desensitizes the transient receptor potential (TRP) channels TRPA1, TRPV1, and TRPV2 [97–99]. Given the synergistic relation between seizures and inflammation [100–102], the cannabinoid system provides a novel strategy to target both segments of this feedback cycle.

CBD

CBD resembles Δ⁹-THC structurally but the 2 molecules differ significantly in pharmacology and function. CBD has very low affinity at CB₁R and CB₂R, unlike Δ⁹-THC [103–106]. The potential targets for CBD are reviewed in detail in another article in this issue (“Molecular Targets of CBD in Neurological Disorders”). CBD is an agonist at TRP channels (TRPV1, TRPV2, TRPA1) [98, 99, 104], 5-hydroxytryptamine_{1α} receptors [107], and glycine receptors [108]. CBD is an antagonist at TRP melastatin type-8 channels [97], T-type voltage-gated calcium channels [109], and G protein-coupled-receptor GPR55 (see below).

CBD exerts dynamic control over intracellular calcium stores through multiple, activity-dependent pathways [110, 111]. CBD induces a bidirectional change in intracellular calcium levels that depends on cellular excitability. Under normal physiological Ca²⁺ conditions, CBD slightly increases intracellular Ca²⁺, whereas CBD reduces intracellular Ca²⁺ under high-excitability conditions. These changes were blocked by the pretreatment with an antagonist of the mitochondrial Na⁺/Ca²⁺ exchanger, suggesting a mitochondrial site of action [111]. CBD also produces biphasic changes in intracellular calcium levels via antagonism of the mitochondrial voltage-dependent anion channel 1 [112].

CBD antagonizes GPR55, which functions as a counterpart to the canonical CB₁R/CB₂R signaling pathway [113]. GPR55 is present in the caudate, putamen, hippocampus, thalamus, pons, cerebellum, frontal cortex, and thalamus. GPR55 was initially characterized as a novel cannabinoid receptor, coupled to Gα₁₃ [114]. Activation of GPR55 in human embryonic kidney cells triggers the release of intracellular Ca²⁺ from endoplasmic reticulum stores via a pathway dependent on RhoA (Ras homolog gene family member A), phospholipase C, and inositol 1,4,5-trisphosphate receptor [115]. The endogenous membrane phospholipid L-α-lysophosphatidylinositol is a GPR55 agonist [116]. Brief application of L-α-lysophosphatidylinositol transiently increases intracellular Ca²⁺ levels and vesicular release probability at excitatory hippocampal synapses. CBD opposes this effect by reducing glutamate release, suggesting a potential antiseizure mechanism [117]. CBD also reduces epileptiform activity (burst amplitude and duration) in *in vitro* (4-aminopyridine and Mg²⁺) models through a CB₁-independent, concentration-dependent, and region-specific manner in the hippocampus. Preclinical studies demonstrate an anti-seizure effect of CBD (see “Preclinical Evidence”).

CBD also regulates several transporters, enzymes, and metabolic pathways that are common to Δ⁹-THC and endocannabinoid signaling. CBD inhibits uptake of adenosine by blocking the equilibrative nucleoside transporter [118, 119]. Increased levels of adenosine activate A₂ receptors, which regulate striatal CB₁Rs [120]. At high micromolar

levels, CBD also inhibits the uptake and enzymatic degradation of anandamide via FAAH, elevating anandamide extracellular concentrations [121]. Thus, dynamic interactions likely occur between the multiple plant cannabinoids such as CBD and Δ 9-THC (see “Entourage Effect”).

CBD limits inflammation and oxidative stress [122]. CBD reduces oxidative toxicity in an *in vitro* glutamate excitotoxicity assay [123], and raises adenosine to oppose lipopolysaccharide-induced inflammation and tumor necrosis factor- α release [118, 124]. In mice with middle cerebral artery occlusion, CBD triggered a CB₁R-independent decrease in reperfusion injury, inflammation, and death. This neuroprotective action may result from reduced myeloperoxidase activity, neutrophil migration, and microglia high-mobility group box 1 expression [125, 126]. Additionally, CBD activates peroxisome proliferator-activated receptor- γ , reduces NO and IL- β release, limits gliosis, and restricts neuroinflammation in mice injected with amyloid β [127–129]. Finally, treatment of microglial cultures with interferon- γ raised mRNA levels of the CBD receptor GPR55 [130], which regulates the inflammatory responses to neuropathic pain [131]. Taken together, these studies suggest that CBD reduces neuroinflammation in several disease-specific conditions.

The “Entourage Effect”

The “entourage effect” was a term originally coined by Ben-Shabat et al. [132] to refer to the potentiating effects of endocannabinoid metabolic byproducts on endocannabinoid function at CB₁Rs and CB₂Rs. They observed that 2 esters of the endocannabinoid 2-AG—s2-linoleoyl-glycerol and 2-palmitoyl-glycerol—were present in spleen, brain, and gut, together with 2-AG. While these esters do not bind to cannabinoid receptors or inhibit adenylyl cyclase via either CB₁ or CB₂, each ester potentiated 2-AG-induced inhibition of motor behavior, immobility on a ring, analgesia on a hot plate, and hypothermia: behavioral tests commonly referred to as the ‘tetrad’ by which CB₁-mediated effects can be detected [132]. Thus, the original concept of the entourage effect referred to a specific group of endogenous compounds, structurally similar to endocannabinoids, that potentiated the effects of endogenous cannabinoid receptor agonists at CB₁Rs and CB₂Rs.

Subsequently, the idea of the entourage effect has expanded considerably both with regard to mechanisms of interactions, as well as classes of chemical agents. The diversification of entourage effects has been promoted by scientific and lay authors, and often well beyond its original boundaries. Wagner and Ulrich-Merzenich [133] proposed 4 potential mechanisms of synergy for phytotherapeutics, using cannabis as an exemplar: 1) multitarget effects; 2) pharmacokinetic effects (e.g., improved bioavailability or solubility); 3) improved bacterial resistance; and 4) modulation of adverse events (AEs;

truly an antagonism, albeit a beneficial one) [133]. This approach thereby extended the tightly defined entourage effect to include practically any plant mixture acting through any molecular target to exert any effect.

The cannabis plant contains a complex mixture of both cannabinoids (i.e., Δ 9-THC and CBD) and terpenoids (limonene, myrcene, α -pinene, linalool, β -caryophyllene, caryophyllene oxide, nerolidol, and phytol) derived from a common precursor (geranyl pyrophosphate). Several studies posited that the “entourage” of “[whole] plants are better drugs than the natural products isolated from them”, suggesting that the clinical effects of cannabis usage may be due to complex interactions between several plant cannabinoids [134, 135]. In support of this view, CBD may potentiate the beneficial effects associated with Δ 9-THC (analgesia, antiemesis, and anti-inflammation) and reduce the negative psychoactive effects of Δ 9-THC (impaired working memory, sedation, tachycardia, and paranoia) [136–138]. Users of cannabis with a high CBD: Δ 9-THC ratio have greater tolerability and lower rates of psychosis than users of high Δ 9-THC:CBD ratios (or Δ 9-THC alone) [139]. Additional reports claim potential synergistic interactions of phytocannabinoids and phytoterpenoids that may include therapeutic effects on pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, fungal, and bacterial infections [135, 140]. However, proper characterization of any “synergistic” effects of multiple plant cannabinoids requires statistically robust demonstrations of effects greater than the sum of the parts. These effects can be tested *in vitro* or *in vivo* using assays such as the isobolographic approach [141, 142]. Such a design can show if any 2 compounds, extracts, or mixtures are additive in the specific assay (e.g., models of seizure), synergistic, or antagonistic, thereby avoiding speculation about potential synergism or the confusion of additive effects with synergism. Although experimental data support the efficacy of both CBD and Δ 9-THC as individual agents in various animal models of epilepsy, we are not aware of any studies demonstrating synergy of these compounds in animal models nor any controlled trials that establish a synergistic effect in patients with epilepsy.

Collectively, several studies demonstrate functional (but not defined molecular) interactions between plant cannabinoids that extended the initial concept of the entourage effect far beyond its original intent. While such interactions may exist, further well-defined research is required to verify anecdotal claims regarding the increased antiseizure efficacy of CBD with Δ 9-THC (*vs* CBD alone) in patients with epilepsy. While natural selection may have led to combinations of phytochemicals in cannabis to resist infection or predation, there is no reason to expect “nature” to combine chemicals in a single plant to treat human epilepsy.

Animal Models of Seizures and Epilepsy

Animal models provide powerful assays to assess the potential antiseizure or antiepileptic effects of cannabinoids. Each preclinical paradigm has unique advantages and disadvantages, and many represent unique seizure etiologies, semiologies, or corresponding electroencephalography (EEG) patterns. Table 1 (adapted from [143–145]) summarizes animal models discussed in this review, grouped by relevance to human epilepsies. Acute models (e.g., kainic acid and pentylenetetrazol) allow high-throughput screening for upregulation of biomarkers, but cannot recapitulate spontaneous recurrent seizures or reduced seizure thresholds found in chronic epilepsy. Chronic models of seizure activity elicit spontaneous, recurrent seizures that can be recorded on video EEG. While technically challenging, these models better represent epileptogenesis and drug screening for humans. However chronic models are specific to the type of insult (traumatic brain injury, mouse genetic models), and may not reflect broad anatomical or functional changes in generalized epilepsy [145].

Preclinical Evidence of Cannabinoids in Epilepsy

Multiple animal models demonstrate the efficacy of cannabinoids in preventing seizures and reducing mortality in epilepsy. Animal models highlight dynamic changes in the endocannabinoid system follow chronic seizures, with both acute and chronic homeostatic regulatory components.

The Endocannabinoid System

Endocannabinoid release prevents seizure-induced neurotoxicity. Kainic acid (KA) (30 mg/kg)-induced seizures increased levels of the anandamide in wild-type mice (20 min postinjection) [146], and pilocarpine (375 mg/kg)-induced seizures increased levels of 2-AG (15 min postseizure onset) [147]. Thus, epileptiform activity triggers a neuroprotective, on-demand release of endocannabinoids (or increase endocannabinoid levels in a downstream pathway unrelated to neuroprotection). Pretreatment with an anandamide reuptake inhibitor (UCM707; 3 mg/kg) reduced KA-induced seizure severity, but not in mice with conditional CB1R deletion in principal forebrain excitatory neurons [146]. Blockade of the endocannabinoid catabolic enzyme FAAH (with AM374; 8 mg/kg) increased levels of anandamide and protected against KA (10 mg/kg)-induced hippocampal seizures and subsequent impairments in balance and coordination [148]. Inhibition of both FAAH (with AM374) and the anandamide reuptake transporter (with AM404) in rat hippocampus prevented α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-induced excitotoxic insults (cytoskeletal damage and synaptic decline) *in vitro* and behavioral and

memory impairment *in vivo* [149]. Blockage of FAAH and DAGL α (with AM6701, 5 mg/kg) raised levels of anandamide and 2-AG, protected against KA (10 mg/kg)-induced seizures, and reduced seizure-induced cytotoxicity [150]. The endocannabinoids, methanandamide, and 2-AG reduced neuronal firing in a low Mg²⁺ *in vitro* model of status epilepticus, in a dose-dependent manner (EC₅₀ 145 ± 4.15 nM methanandamide, 1.68 ± 0.19 μ M 2-AG) [151].

CB₁Rs

Animal models demonstrate that activation of CB₁Rs reduces seizure severity. Mice with conditional deletion of CB₁Rs in principal forebrain excitatory neurons (but not interneurons) exhibited more severe KA-induced seizures (30 mg/kg) than wild-type controls. Conditional deletion of the CB₁R increased gliosis and apoptosis following KA-induced seizures and prevented activation of the protective immediate early genes (c-Fos, Zif268, brain-derived neurotrophic factor) [146]. CB₁R expression in hippocampal glutamatergic (but not GABAergic) inputs is necessary and sufficient to protect against KA-induced seizures [152]. Further, viral-induced overexpression of CB₁Rs targeted to the hippocampus reduced KA-induced seizure severity, seizure-induced CA3 pyramidal cell death, and mortality [153]. Together, these results demonstrate that CB₁Rs could limit seizure activity and protect neurons from subsequent cell death and reactive gliosis.

Seizures trigger homeostatic changes in hippocampal CB₁Rs and the endocannabinoid system (reviewed in [154]) (Fig. 3). Levels of CB₁R expression in the CA1-3 stratum oriens and radiatum (presumed excitatory inputs) and dentate gyrus steadily increased 1-week post-pilocarpine-induced seizures (Fig. 3, dark green trace) [147, 155–158]. However, sclerotic and nonsclerotic hippocampal tissue resected from patients with epilepsy displayed a reduction in DAGL α (2-AG biosynthetic enzyme), CB₁R mRNA, and CB₁R excitatory terminal immunoreactivity (Fig. 3, light green trace) [159]. Furthermore, compared with healthy controls, patients with temporal lobe epilepsy have reduced levels of anandamide in cerebrospinal fluid samples [160]. These findings suggest that seizure activity induces a homeostatic upregulation of excitatory terminal CB₁Rs, which may reduce excitatory neurotransmitter release via DSE (see “The Endocannabinoid System”). This compensatory process may be impaired in patients with prolonged treatment-resistant epilepsy or hippocampal sclerosis, leading to neuronal hyperexcitability, pharmacoresistance, and inconsistent effects of cannabis exposure. However, further research is required to verify the functional effects of this potential process in human patients, and whether CB₁R homeostasis indeed limits seizure severity or occurrence.

In contrast to effects at excitatory terminals, seizures induce a homeostatic reduction in CB₁R expression in inhibitory

Table 1 Preclinical animal models of seizures (adapted from [143–145])

Type of seizure model	Method	Mechanism	Relevant human condition	Common use
Acute	MES	Electrical stimulation	Generalized tonic-clonic seizure	Drug screening (used as a first-line screening method for AEDs)
Acute	PTZ	GABA _A R antagonist, Ca ²⁺ channels (?), Na ⁺ channels (?)	Generalized seizure	Drug screening (used as a first-line screening method for AEDs), seizure mechanism
Acute	KA	Ionotropic glutamate receptor (e.g., AMPAR, kainate receptor agonist)	Focal (temporal lobe) seizure	Drug screening, mechanism of seizures/epileptogenesis and cognitive impairments
Acute	Flurothyl	GABA _A R antagonist	Multiple acute seizures, childhood epilepsy	Development of cognitive impairments from early life seizures
Acute	Other chemoconvulsant (e.g., bicuculline, 3-MPA, picrotoxin, etc.) Hypoxia/ischemia	Various	Generalized seizures (or focal, if applied locally)	Drug screening
Acute		Anoxic depolarization, impaired Na ⁺ /K ⁺ ATPase, ↑ extracellular impairments K ⁺ /[glutamate]/[aspartate], ↑ intracellular Na ⁺ , Ca ²⁺	Hypoxic–ischemic encephalopathy	Age-specific (e.g., neonatal) drug screening, mechanisms of seizures and cognitive impairments
Acute	Hyperthermia	Activation of temperature-sensitive ion channels, release of proinflammatory cytokines	Febrile seizures	Drug screening, long-term consequences of seizures
Chronic with high propensity for induced seizures	Lithium/pilocarpine-induced chemical kindling	AChR agonist	Focal (temporal lobe) seizures	Drug screening, mechanism of seizures/epileptogenesis and cognitive impairments
Chronic with high propensity for induced seizures	Electrical (e.g., 6Hz psychomotor, limbic) kindling	Electric stimulation	Focal (temporal lobe) seizures	Drug screening, mechanism of seizures/epileptogenesis and cognitive impairments
Chronic epilepsy (SRS)	Stroke, TBI	Disease-specific models	Focal epilepsy	Drug screening, mechanism of seizures/epileptogenesis and cognitive impairments
Chronic epilepsy (SRS)	SE	Chronic treatment with KA or pilocarpine	Prolonged seizures	Drug screening
Chronic epilepsy (SRS)	Genetic (e.g., GAERs, WAG/lj mice, photosensitive baboons)	Various	Specific seizure models (e.g., absence seizures, genetic)	Drug screening

SRS = spontaneously recurring seizures; MES = maximal electroshock; PTZ = pentylenetetrazole; KA = kainic acid; 3-MPA = 3-mercaptopropionic acid; TBI = traumatic brain injury; SE = status epilepticus; GAERs = genetic absence epilepsy rats from Strouberg; GABA_AR = γ -aminobutyric acid type A receptor; AMPAR = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ATPase = adenosine triphosphatase; AChR = acetylcholine receptor; AEDs = antiepileptic drugs

terminals (Fig. 3, dark red trace). Beginning 4 days following pilocarpine-induced seizures in rats, CB₁R expression progressively decreased in hippocampal CCK+ inhibitory nerve terminals [161], particularly in the CA1 stratum pyramidale and the dentate gyrus inner molecular layer, unaccounted for by CA1 neuronal cell loss alone [155, 156, 162]. By reducing CB₁R expression on inhibitory terminals (and presumed DSI), this homeostatic process may limit network disinhibition and restrain elevated excitability during prolonged epileptiform activity. In sclerotic hippocampal tissue removed from 1) 2 months post pilocarpine-induced seizures in mice [163], and 2) human patients [164], levels of CB₁R remained consistently elevated in interneuron axonal terminals (Fig. 3, light red trace). This finding suggests that patients with prolonged, pharmaco-resistant epilepsy may suffer from impaired CB₁R homeostasis on inhibitory interneuron terminals, leading to prolonged disinhibition and network excitability. Postseizure changes in CB₁R may be specific to seizure type or developmental stage, as mice with a single episode of febrile seizures induce an overall increase in DSI and CB₁R on CCK+ interneurons [165, 166].

Modulators of the Endocannabinoid System and Synthetic CB₁R Agonists/Antagonists

Figure 4 summarizes the effects of synthetic cannabinoids and phytocannabinoids in 175 pre-clinical seizure models or discrete conditions (adapted from [167]). These studies are subclassified by drug type and seizure model in corresponding tables in the Appendix (see [Supplementary Material](#)).

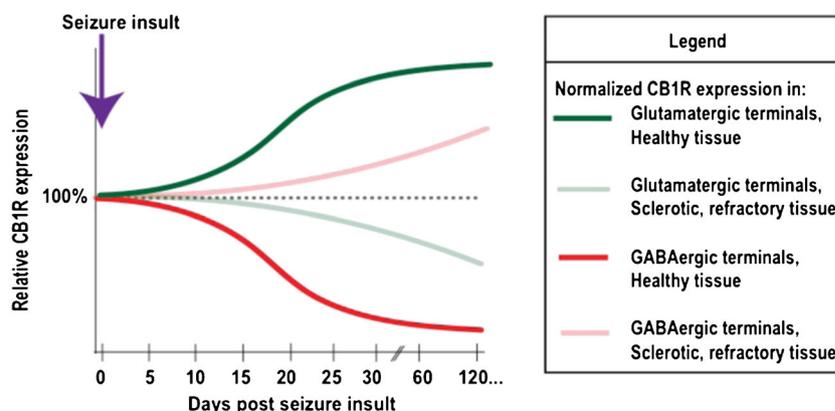
Results from 13 studies from 3 species (rat, mouse, guinea pig) demonstrate that modulation of the endocannabinoid system (via inhibition of FAAH or anandamide reuptake) provides about 46.2 % (6/13) anticonvulsant, 23.1 % (3/13) mixed effect, and 30.8 % (4/13) no significant effect in seizure models. CB₁R agonists produced an anticonvulsant effect in 68.1 % (47/69), proconvulsant effect in 2.9 % (2/69), mixed effect in 7.2 % (5/69), and no significant effect in 21.7 % (15/69) of seizure models in rats and mice. One study suggests that

CB₁R agonists may produce an anticonvulsant effect through CB₁R at low doses, but a proconvulsant effect through TRPV1 channels at high doses [168]. In addition, CB₁R agonists (WIN55, 212, ACEA) often produce an additive effect when combined with several commonly prescribed AEDs (see Fig. 4B) [169–177]. In 18 studies from mice, rats, and guinea pigs, CB₁R antagonists were proconvulsant in 38.9 % (7/18), anti-convulsant in 5.6 % (1/18), and showed no significant effect in 55.6 % (10/18) of trials. Although CB₁R agonists were anticonvulsant in 68.1 % of the studies, only 38.9 % of CB₁R antagonists were proconvulsant (most showed no effect). Thus, while activation of the endocannabinoid system may prevent long-term consequences of seizure sequelae, inhibition of the endogenous protective mechanisms may not contribute significantly to seizures. Variations in the pro- vs anticonvulsant effects in each system may reflect specific effects of the species, seizure models (acute vs chronic, focal vs generalized), dose ranges, timing, or experimental design.

Phytocannabinoids: Δ 9-THC and CBD

Evidence from 34 studies from 6 animal species demonstrate that Δ 9-THC is anticonvulsant in 61.8 % (21/34), proconvulsant in 2.9 % (1/34), mixed in 2.9 % (1/34), and shows no significant effect in 32.4 % (11/34) of seizure models. Δ 9-THC potentiated the effects of phenytoin and phenobarbital in the maximal electroshock model of generalized seizures [178, 179]. The National Toxicology Program noted a proconvulsant effect of Δ 9-THC in rats and mice [180], although species-specific differences in CB₁R expression may underlie variable responses to Δ 9-THC. CBD and its homologue cannabidiol (CBDV) were 80.5 % (33/41) anticonvulsant and 19.5 % (8/41) ineffective, at reducing seizures in mice and rats. Notably, no studies showed a proconvulsant effect for CBD or CBDV. CBDV potentiated the effects of phenobarbital, ethosuximide, and valproate in 2 seizure models [181]. These studies suggest that both Δ 9-THC and CBD provide significant protection from seizures

Fig. 3 Homeostatic changes to hippocampal cannabinoid type 1 receptors (CB₁R) in preclinical animal seizure models [147, 154–166]. GABA = γ -aminobutyric acid



in preclinical animal trials, presenting potential targets for human studies.

Tolerance and Withdrawal

Prolonged treatment with Δ 9-THC or synthetic CB1 agonists leads to a dose-dependent and region-specific desensitization, downregulation, and internalization of CB₁Rs [182–203]. These changes produce tolerance to the acute behavioral effects of Δ 9-THC in *in vivo* models, reducing cannabinoid-induced hypomotility, hypothermia, antinociception, and memory impairment with repeated usage [182, 183, 185, 197, 199, 204, 205]. In several seizure models, prolonged Δ 9-THC (but not CBD) exposure leads to tolerance to the antiepileptic activity of cannabinoids [206–210]. In humans, chronic cannabinoid usage produces tolerance towards Δ 9-THC-mediated changes in autonomic behaviors, sleep and sleep EEGs, and self-reported psychotropic high, although these changes vary in frequent users [211–216].

Withdrawal from rats chronically dosed with Δ 9-THC triggers rebound seizures and elevated anxiety-like responses in several preclinical animal studies [217–219]. Monkeys that previously self-administered intravenous Δ 9-THC demonstrate abstinent symptoms of aggressiveness, hyperirritability, and anorexia [220], as well as impaired operant behavior [221]. Results from human studies demonstrated symptoms of anxiety, aggression, dysphoria, irritability, anorexia, sleep disturbances, and sweating during abstinence from chronic Δ 9-THC usage, rescued by Δ 9-THC re-administration [222]. Withdrawal from cannabis use can trigger rebound seizures in several preclinical animal and human studies [203, 209, 210, 223–226], although other studies show no proconvulsant effect of cannabis withdrawal [178, 227].

Unlike Δ 9-THC, CBD (or nabiximols, CBD/ Δ 9-THC in a 1:1 ratio) does not seem to produce significant intoxication [228], tolerance [229–231], or withdrawal effects [232]. CBD and/or nabiximols may counteract the Δ 9-THC-dominant effects of cannabis withdrawal [233–235]. In summary, evidence suggests that while both tolerance and some withdrawal symptoms may occur with Δ 9-THC, CBD may limit the effects of cannabis tolerance and withdrawal, but more studies are needed.

Clinical Evidence of Cannabinoids in Epilepsy

Several clinical studies have examined the association between cannabis use and seizures. These include case studies, surveys and epidemiological studies, and clinical trials.

Case Studies

Case reports describe proconvulsant and anticonvulsant effect of cannabis, with the majority reporting either beneficial or

lack of effect on seizure control. Selected examples illustrate the diverse spectrum of reported responses. Cannabis used 7 times within 3 weeks was associated with multiple tonic–clonic seizures in a patient previously seizure free for 6 months on phenytoin and phenobarbital. However, seizures were not temporally correlated with immediate intoxication or withdrawal [236]. Cannabis withdrawal increased complex partial seizure frequency in a 29-year-old man with a history of alcoholism and bipolar disorder (each of which are independently associated with seizures) [226]. In another 2-part case study, a 43-year-old on carbamazepine experienced about 5–6 nightly violent seizures lasting 1 min each. When he consumed about 40 mg *C. sativa* at night, seizure frequency was reduced by 70 %, but withdrawal triggered a doubling of his baseline seizure frequency. In the same study, a 60-year-old man with a 40-year history of cannabis usage (6–8 cigarettes per day) developed status epilepticus after cannabis withdrawal [225]. Additionally, synthetic “designer” cannabinoid drugs (“spice” or “K2”) induce new-onset seizures, tachyarrhythmia, and psychosis, often with greater severity and toxicity than cannabis [237–245]. The toxicity of these synthetic agents may result from their properties as full agonists of CB₁R, while Δ 9-THC is a partial agonist.

The majority of other studies demonstrate an anticonvulsant effect of cannabis. In a 1949 trial, administration of a Δ 9-THC homolog (1,2-dimethyl heptyl) reduced the “severe anticonvulsant resistant (phenobarbital or phenytoin) grand mal epilepsy” in 2/5 children [246]. One patient whose seizures were not controlled on low-dose phenobarbital or phenytoin had fewer tonic–clonic seizures while smoking 2–5 cannabis cigarettes per day [247]. Myoclonic and other seizures were reportedly reduced in 3 adolescents on oral 0.07–0.14 mg/kg Δ 9-THC daily. Parents reported that their children were “more relaxed...more alert, more interested in her surroundings” [248]. In another study, a 45-year-old man with cerebral palsy and treatment-resistant focal epilepsy experienced a marked reduction in focal and secondary generalized seizures on daily marijuana [249]. Other recent cases also support the observation that cannabis use can reduce seizures in some patients [250, 251]. These studies suggest that cannabis can not only reduce seizure susceptibility, but also trigger rebound seizures during withdrawal. Limitations of open-label, often retrospective single case reports are compounded by the variability in epilepsy syndrome, differences in cannabis dosage, route, and composition.

Epidemiological Reports and Surveys

Recent epidemiological reports and surveys depict the incidence of medical marijuana usage for seizure control. The predicted prevalence of medical cannabis use in epileptic patients ranges from about 4 % (77=total patient population in US medical cannabis program) to about 20 % (310=total patients at a tertiary

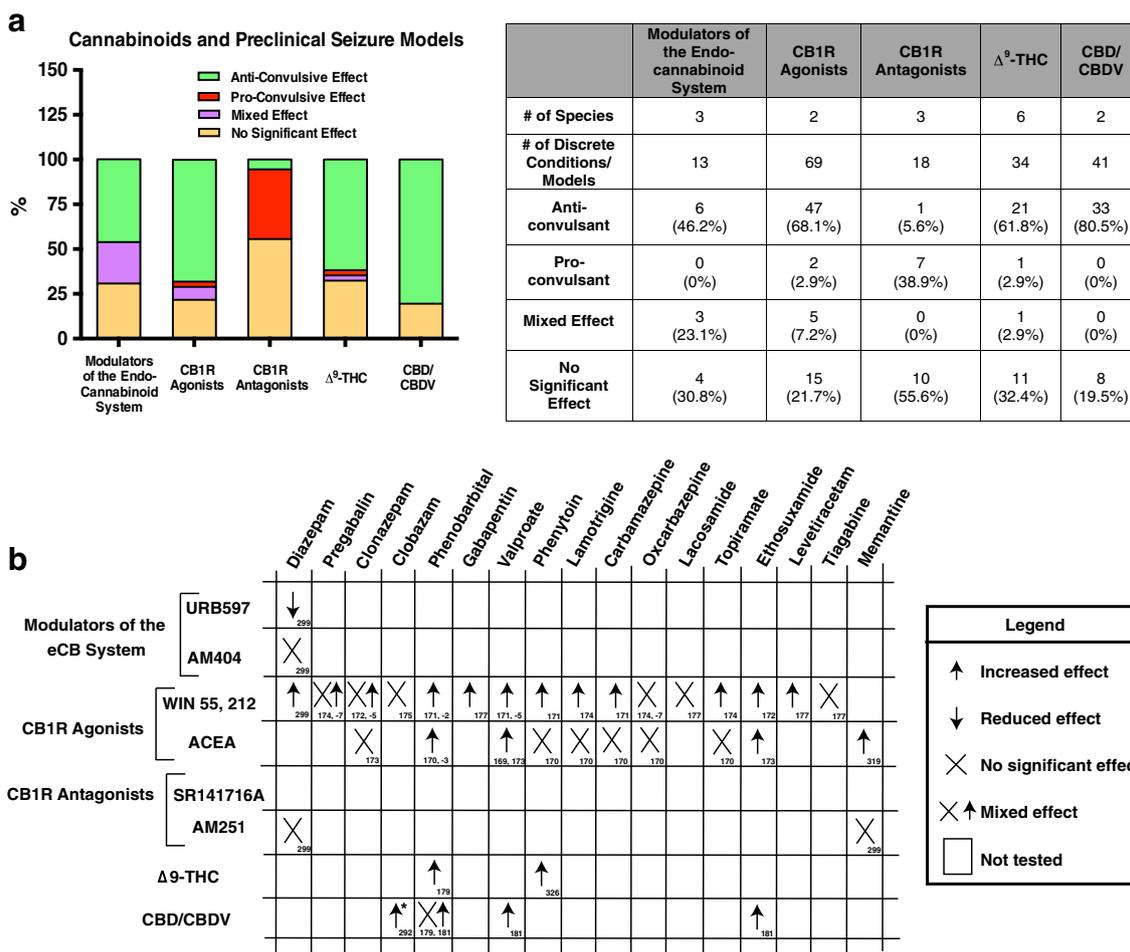


Fig. 4 Summary of cannabinoids and preclinical seizure models. (A) Composite data from 175 preclinical seizure models (e.g., maximal electroshock, kainic acid) or discrete experimental designs (e.g., with combined antiseizure medications). Pro-/antiseizure effects are subclassified by given intervention: 1) modulators of the endocannabinoid (eCB) system (e.g., fatty acid amide hydrolase inhibitor URB597); 2) cannabinoid type 1 receptor (CB₁R) agonists (e.g., WIN55212-2); 3) CB₁R antagonists (e.g., SR141716A); 4) Δ⁹-

tetrahydrocannabinol (Δ⁹-THC); and 5) cannabidiol (CBD)/cannabidivarin (CBDV). (See [Supplementary Material](#) for complete description of preclinical studies.) (B) Summary of preclinical data on cannabinoid interactions with antiseizure medications. Sources indicated in boxes. *Recent evidence from a phase I clinical trial suggests that CBD/CBDV elevates serum concentrations of clobazam and N-desmethyloclobazam in human pediatric patients with treatment-resistant epilepsy [292]. ACEA = arachidonyl-2'-chloroethylamide

epilepsy clinic in Germany) [252, 253]. One percent of the medical marijuana users in California (~2500=total patient population) use cannabis to control seizures [254]. In a telephone survey of 136 patients with epilepsy, 21.0 % were active users, 13.0 % were frequent users, 8.1 % were heavy users, and 3.0 % met Diagnostic and Statistical Manual of Mental Disorders-IV criteria for marijuana dependence.

The majority of patient and caregiver surveys found either beneficial effects or no significant effect of cannabis in patients with epilepsy. In a small, 1976 survey of 300 patients with epilepsy, cannabis usage had no effect on seizure frequency in 30 % of patients, increased seizures in 1 patient, and decreased seizures in another [255]. A 1989 12-year retrospective study reported 10 % of 47 patients with “recreational drug-induced [tonic-clonic] seizures” had consumed cannabis prior to seizures, although this was confounded by recent cocaine, amphetamine, or LSD

(lysergic acid diethylamide) usage. No seizures were reported following cannabis use alone [256]. A single epidemiological study provided limited evidence that cannabis may possess anti-seizure properties in humans. In a study of illicit drug use and new-onset seizures in Harlem utilizing a case-control methodology, cannabis used within 90 days before hospitalization was associated with a 2.8-fold decreased risk of first seizures among men but not women [257]. In a telephone survey of adult patients from a tertiary care epilepsy center, most active users reported beneficial effects on seizures (68 % reduced severity, 54 % reduced incidence), and 24 % of all subjects believed marijuana was an effective therapy for epilepsy. No patient reported a worsening of seizures with cannabis use [258]. The majority (84 %) of patients in a German tertiary care center reported that cannabis had no effect on their seizure control [253].

A 2013 survey of 19 parents of children with treatment-resistant epilepsy investigated the use of high CBD:Δ9-THC ratio artisanal marijuana products. These parents were primarily identified from social media and included 12 children with Dravet syndrome (DS). Of the 12 children with DS, parents reported that 5 (42 %) experienced a >80 % reduction in seizure frequency and 2 (11 %) reported complete seizure freedom. The single child with Lennox–Gastaut syndrome (LGS) was reported to have a >80 % reduction in seizure frequency. In addition to seizure control, parents reported positive effects of increased alertness (74 %), better mood (79 %), improved sleep (68 %), and decreased self-stimulation (32 %), and rare AEs of drowsiness (37 %) and fatigue (16 %) [259]. A more recent retrospective case study described 75 patients from Colorado with treatment-resistant epilepsy who moved to Colorado for oral cannabis extract treatment. Oral cannabis extract treatment controlled seizures in 57 % of patients, reduced seizures by >50 % in 33 % of patients, and showed greater effectiveness in patients with LGS (88.9 %) than in patients with DS (23.0 %). Reported additional benefits included improved behavior/alertness (33 %), language (10 %), and motor skills (10 %), as well as rare AEs of increased seizures (13 %) and somnolence/fatigue (12 %). Interestingly, the study also reported a significant, independent “placebo effect” of families moving to Colorado for treatment (see “Placebo Effect”) [260]. Collectively, these surveys suggest a predominantly antiseizure (or no significant) effect of cannabis usage. However, it is essential to consider the limitations of subjective self-reporting, potentially biased sampling of patient advocacy groups (over-reporting positive effects), and uncontrolled differences in CBD:Δ9-THC content in various strains of cannabis in these studies.

Clinical Trials

A recent Cochrane review assessed 4 primary clinical trials to examine the efficacy of medical marijuana in seizure control (summarized in Table 2, adapted from [11], [13]). Two of these studies demonstrated a partial antiseizure effect of CBD [261, 262], while 2 showed no significant effect [263, 264]. However, all 4 studies included significant limitations, including low study sizes, insufficient blinding or randomization, or incomplete data sets. The authors of the Cochrane review and a recent meta-analysis from the American Academy of Neurology both emphasized the need for follow-up placebo-controlled, blinded, randomized clinical trials examining the role of CBD in seizure control [12, 13].

Phase I Clinical Trial for CBD in Treatment-resistant Epilepsy

Preliminary preclinical and clinical evidence reveal the therapeutic potential of CBD to reduce seizures with high

tolerability and low toxicity. Accordingly, CBD represents a highly desirable treatment alternative for patients with early-onset, severe epilepsy such as DS and LGS. In addition to pharmacoresistant seizures, these patients suffer from severe neurodevelopmental delay, intellectual disability, autism, motor impairments, and significant morbidity and mortality [265, 266]. As patients with DS and LGS require effective and better-tolerated therapies and represent relatively homogeneous populations, they stand out as candidates for an initial trial of CBD safety and efficacy.

Study Design and Results

Investigator-initiated open-label studies at 10 epilepsy centers using Epidiolex (GWPharma, Salisbury, UK; 99 % CBD) collected data on 213 patients with treatment-resistant epilepsies. This predominantly pediatric population had a mean age of 10.8 years (range 2.0–26.0 years). CBD was added to existing AEDs; there was an average of 3 concomitant AEDs. The average baseline was 60 per month for total seizures and 30 per month for convulsive seizures.

The primary goal of the study was to assess safety but seizure diaries were obtained for convulsive, drop, and total seizures to provide a potential signal regarding efficacy. Twelve-week or longer continuous exposure data were obtained for 137 patients and were used in efficacy measures. The most common epilepsy etiologies were DS and LGS syndromes; others included Aicardi syndrome, Doose syndrome, tuberous sclerosis complex, CDKL5, Dup15q syndrome, and many others. At week 12, total convulsive and nonconvulsive seizures showed a median percent reduction from baseline of 54 %, and total convulsive seizures showed a median percent reduction from baseline of 51 %. In patients with DS ($n=23$), CBD reduced convulsive seizure frequency by 53 %, and 16 % of DS reached complete convulsive seizure freedom by week 12. Atonic seizure frequency among patients with LGS ($n=10$) was reduced by a median of 52 % at week 12. AEs >10 % included somnolence (21 %), diarrhea (17 %), fatigue (17 %), and decreased appetite (16 %). Nine patients (4 %) were discontinued for AEs. The investigators concluded that CBD reduced seizure frequency across multiple drug-resistant epilepsy syndromes and seizure types and was generally well-tolerated in the open-label study. Randomized controlled trials (RCTs) are now ongoing for DS and LGS.

Safety Issues

There is a strong tendency to equate “cannabis as a natural therapy” with “cannabis as a safe therapy”. This a priori assumption—the naturalistic fallacy—is countered by many instances of toxic or deadly plants (e.g., amatoxins in mushrooms) and animals (e.g., tetrodotoxin in puffer fish). A more muted naturalistic view is that if side effects occur with

cannabis, they would be less severe than those from drugs produced by the pharmaceutical industry. A recent *Epilepsia* survey of 776 individuals found that 98 % of the general public supported the use of medical marijuana for severe cases of epilepsy, compared with only 48 % of epileptologists. Similarly, the majority of the public and a minority of epileptologists thought that there was sufficient safety (96 % vs 34 %) and efficacy (95 % vs 28 %) data for medical marijuana use in severe epilepsy. This significant disparity in opinion between professionals and the lay public, possibly swayed by the appeal of natural remedies, emphasizes an increased need for further research and public education regarding medicinal cannabis and epilepsy [267].

As with efficacy, the most valid assessment of side effects is with RCTs. RCT data on the safety of Δ 9-THC and CBD in adults comes from trials of cannabinoid-containing medications, including nabixomols [Sativex (GWPharma) 1:1 Δ 9-THC:CBD], purified cannabis extracts [Cannador, Institute for Clinical Research, IKF, Berlin, Germany, (2:1 Δ 9-THC:CBD)], synthetic Δ 9-THC analogues Dronabinol and Nabilone. These drugs have been approved by many international regulatory agencies. In a meta-analysis of 1619 patients treated with nabiximols for neurological indications (mainly pain, spasticity, spasm, or tremor) for 6 months or less, 6.9 % of those on cannabinoid therapies were discontinued because of adverse effects versus 2.25 % in the placebo groups [12]. Adverse effects occurring in at least 2 studies included nausea, dizziness, increased weakness, behavioral or mood changes, hallucinations, suicidal ideation, fatigue, and feeling of intoxication. No deaths from overdose were reported [12]. However, our knowledge on the safety of these compounds in children is very limited.

The adverse health effects of recreational cannabis use were recently reviewed [268]. Δ 9-THC is presumed to be the major cannabinoid resulting in adverse acute and chronic health effects of cannabis. The 4-fold increase in Δ 9-THC content of confiscated cannabis in the last 20 years is associated with increased acute complications. In 2011, there were 129,000 emergency department visits for cannabis alone and 327,000 additional visits for cannabis in combination with other drugs. From 2004 to 2011, the rate of emergency department visits for cannabis toxicity doubled [268]. Short-term use can impair short-term memory, coordination, and judgment. In high doses, paranoia and psychosis can occur [137, 269]. Long-term use of recreational cannabis in adolescents is associated with addiction (9 % overall but 17 % among adolescents) and impaired cognitive and academic performance [270–274]. Additionally, cannabis treatment in animal and human studies altered brain development (especially with use in early childhood) and structure [272, 275–277], creating long-lasting functional and structural brain abnormalities [277–279]. Early and/or heavy cannabis use is associated with neurochemical abnormalities on magnetic resonance spectroscopy [272], impaired maintenance of neuronal cytoskeleton dynamics [277], decreased white matter development or integrity

[272, 275, 276], increased impulsivity [276], and abnormal activation patterns during cognitive tasks on functional magnetic resonance imaging [272, 280]. In patients with multiple sclerosis, use of cannabis is associated with impaired cognition and activation patterns on functional magnetic resonance imaging [281]. Further research is required to determine the short- and long-term effects of CBD alone, which may have lower toxicity than whole plant cannabis or Δ 9-THC.

Cannabidiol Formulations, Pharmacokinetics, Pharmacodynamics, and Drug–Drug Interactions

We are aware of 3 pharmaceutical products that are currently in trials or in development: 1) Epidiolex (99 % CBD derived from *C. sativa* plants, in a strawberry-flavored sesame oil), 2) synthetic CBD from Insys Therapeutics (Chandler, AZ, USA), and 3) Transdermal CBD gel from Zynerva Pharmaceuticals (Devon, PA, USA). Other CBD-containing products are available commercially and obtained online [e.g., Realm of Caring's Charlotte's Web (whole cannabis extract containing 50 mg/ml CBD)]. However, the quality control and consistency of these products may vary considerably. Indeed, a recent study by the US Food and Drug Administration tested 18 products, claimed to contain CBD, made by 6 companies. Of these, 8 contained no CBD, 9 contained <1 % CBD, and 1 contained 2.6 % CBD (<http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm435591.htm>).

Because lipophilic cannabinoids (including CBD) have low water solubility, CBD is traditionally delivered orally in either an oil-based capsule or sublingual spray, permitting less variable pharmacokinetics in gastrointestinal absorption. A single 10-mg dose of nabiximols (equal parts CBD and Δ 9-THC) in humans produces a maximum serum concentration (C_{\max}) of $3.0 \pm 3.1 \mu\text{g/l}$ (buccal) [$2.5 \pm 1.8 \mu\text{g/l}$ (sublingual)] and maximum time (T_{\max}) of $2.8 \pm 1.3 \text{ h}$ (buccal) [$1.6 \pm 0.7 \text{ h}$ (sublingual)] [282]. CBD is primarily protein-bound in the blood, and preferentially deposits in brain and adipose tissue [283].

The cannabinoids are primarily metabolized by the liver cytochrome P-450 (CYP-450) enzymes. Both Δ 9-THC and CBD can inhibit CYP-450 metabolic activity, particularly the CYP2C isozymes at low concentrations and CYP3A4 isozymes at higher concentrations [284–289]. CYP2C and CYP3A4 are induced by carbamazepine, topiramate, and phenytoin, and inhibited valproate and other drugs [290]. The cannabinoids, particularly CBD, can inhibit other isozymes, including 2D6 and 1A1 [285, 291]. Therefore, use of Δ 9-THC or CBD could potentially contribute to bidirectional drug–drug interactions with antiepileptic and other drugs. In our open-label CBD study, patients treated with CBD had elevated levels of the nordesmethyl metabolite of clobazam [292], which may account for a portion of the apparent sedation, as well as efficacy, of CBD.

Table 2 Clinical trials of cannabidiol (CBD) and epilepsy (adapted from [11, 13])

Study	Seizure type	Population size	Treatment (subjects per group)	Continued AEDs?	Duration	Outcome	Toxicity	Limitations
Mechoulam and Carlini [261]	Treatment-resistant, temporal lobe epilepsy	9	CBD, 200 mg/day (4) Placebo (5)	NS	3 months	CBD: seizure free (2), partial improvement (1), no change (1); placebo: no change (4)	None	No baseline seizure frequency; no definition of improvement; unclear if AEDs were changed; not truly randomized or blinded; unknown if groups were matched
Cunha et al. [262]	Treatment-resistant, temporal lobe epilepsy	15*	CBD 200–300 mg/day (8*) Placebo (8*)	Yes	3–18 weeks	CBD: near seizure freedom (4), partial improvement (3), no change (1); placebo: no change (7), partial improvement (1)	Somnolence	Not clearly blinded (1 patient transferred groups); doses were adjusted in CBD group, not in placebo; CBD group received longer average treatment
Ames and Cridland [263]	Treatment-resistant epilepsy, intellectual/developmental disability	12	CBD 300 mg/day for 1 week; 200 mg/day for 3 weeks (6?) Placebo (6?)	NS	4 weeks	No difference between CBD and placebo	Somnolence	Brief letter to the editor, details lacking on specifics; discontinued owing to “technical difficulties in preparing the drug”
Tremblay and Sherman [264]	Treatment-resistant epilepsy	10–12†	CBD 100 mg once daily Placebo	Yes	3 months baseline, 6 months CBD or placebo, then 6 months crossover to alternative treatment	No difference between CBD and placebo (seizure frequency or cognitive/behavioral tests)	None	Differences in sample size reporting; data reported are incomplete (conference abstract)‡

AEDs = antiepileptic drugs; NS = not stated

*1 patient switched groups after 1 month

† Abstract and subsequent book chapters have different numbers

‡ Only truly double-blind study

Placebo Effect

The magnitude of the placebo response is related to the power of belief. Given the social and mainstream media attention selectively reporting dramatic benefits of artisanal cannabis preparations for children with epilepsy, there are high expectations on the part of many parents. The potent role of the placebo response was suggested by a recent survey of parents whose children with epilepsy who were cared for at Colorado Children's Hospital. A beneficial response (>50 % seizure reduction) was reported 3 times more often by parents who moved to the state compared with those who were long-time residents [260]. No differences in epilepsy syndrome, type of artisanal preparation, or other factor could account for this difference.

While studies have reported a significant placebo response in adult patients (such as those with Parkinson's Disease [293]), placebo response rates are particularly high among children and adolescents in a subset of disorders, including psychiatric (anxiety, major depression, and obsessive compulsive and attention deficit disorders), medical (asthma), and painful (migraine, gastrointestinal) conditions [294, 295]. As the current RCTs of CBD primarily target children with severe epilepsy, this may be an important issue. Among patients with treatment-resistant focal epilepsy, a meta-analysis found that the placebo response in children (19.9 %) was significantly higher than in adults (9.9 %), while the response to the AED was not statistically different in children (37.2 %) and adults (30.4 %) [296]. In one predominantly pediatric LGS trial, seizures were reduced in 63 % of placebo-treated patients and 75 % of drug-treated patients [297]. Paradoxically, the intense interest and strong beliefs in the efficacy of cannabis for epilepsy may elevate placebo responses and make it more difficult to demonstrate a true benefit in RCTs.

Legal/Ethical Concerns

The Drug Enforcement Agency (DEA) classifies cannabis and products derived from cannabis plants as Schedule I drugs. Schedule I drugs have a high potential for abuse and no currently accepted medical use; they are the most dangerous drugs of all the drug schedules with potentially severe psychological or physical dependence (DEA website; <http://www.dea.gov/druginfo/ds.shtml>). It is thus paradoxical that opiates and benzodiazepines, which have a much greater potential for psychological and physical dependence than cannabis, are classified as Schedule II drugs. With regard to the DEA's "claim" that cannabis-derived drugs have no currently accepted medical use, therapies such as nabiximols (CBD and Δ^9 -THC) and other products have been approved by regulatory agencies in >20 countries. These approvals are based on RCTs that establish efficacy and a favorable safety profile, including a low potential for abuse [228, 298].

The Schedule I categorization makes it challenging for investigators to study cannabis-derived cannabinoids in basic and clinical science. There is often a long and costly process to secure approvals and inspections to obtain cannabinoids, purchase a large safe, the weight of which may require clearance from engineers, and add security systems to the room and building in which they are stored. The Schedule I designation often prevents patients who live in developmental centers or residential homes from participating in clinical trials. The threshold of effort for basic and clinical investigators to study cannabinoids remains as high as ever, while the availability of these substances for parents to give is expanding rapidly. This has created a widening gap between knowledge and exposure, an especially relevant concern in children for whom safety data are largely lacking.

Conclusion

For over a millennium, pre-clinical and clinical evidence have shown that cannabinoids such as CBD can be used to reduce seizures effectively, particularly in patients with treatment-resistant epilepsy. However, many questions still remain (see Box 1) regarding the mechanism, safety, and efficacy of cannabinoids in short- and long-term use. Future basic science research and planned multicenter, placebo-controlled clinical trials will provide insight into cannabinoid function and the potential neuroprotective effects of the endocannabinoid system. These findings will increase our mechanistic understanding of seizures and may provide novel, targeted therapeutics for epilepsy.

Box 1 Unanswered questions and directions for future studies

1. How do the pro and anti-epileptic effects of cannabis change with development? Are there age-specific differences in responsiveness, side effects, and target receptor expression?
 2. What are the long-term effects of cannabis/cannabidiol use?
 3. Are certain types of seizures or genetic channelopathies more likely to respond to cannabidiol than others?
 4. What is the safety of cannabidiol in patients with special conditions (pregnancy, recent or planned surgery, vagus nerve stimulation, etc.)?
 5. How do synthetic cannabinoids ("spice" or "K2") dysregulate the central nervous system to induce seizures? What is their relative safety and toxicity relative to cannabis?
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References

1. Fisher RS, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005;46:470-472.
2. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314-319.
3. Kwan P, Brodie MJ. Refractory epilepsy: a progressive, intractable but preventable condition? *Seizure* 2002;11:77-84.
4. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. *N Engl J Med* 2011; 365:919-926.
5. Nilsson L, et al. Risk factors for sudden unexpected death in epilepsy: a case-control study. *Lancet* 1999;353:888-893.
6. Walczak TS, et al. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. *Neurology* 2001;56:519-525.
7. Devinsky O. Patients with refractory seizures. *N Engl J Med* 1999;340:1565-1570.
8. Jacoby A, Baker GA. Quality-of-life trajectories in epilepsy: a review of the literature. *Epilepsy Behav* 2008;12:557-571.
9. Rogawski MA. The intrinsic severity hypothesis of pharmacoresistance to antiepileptic drugs. *Epilepsia* 2013;54(Suppl. 2):33-40.
10. Perucca E. Is there a role for therapeutic drug monitoring of new anticonvulsants? *Clin Pharmacokinet* 2000;38:191-204.
11. Devinsky O, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia* 2014;55:791-802.
12. Koppel BS, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2014;82:1556-63.
13. Gloss D, Vickrey B. Cannabinoids for epilepsy. *Cochrane Database Syst Rev* 2014; 3:CD009270.
14. Abel EL. Marijuana: the first twelve thousand years. Plenum Press, New York, 1980.
15. Russo EB, et al. Phytochemical and genetic analyses of ancient cannabis from Central Asia. *J Exp Bot* 2008;59:4171-4182.
16. Lozano I. The therapeutic use of *Cannabis sativa* L. in Arabic medicine. *J Cannabis Ther* 2001;1:63-70.
17. Szaflarski JP, Bebin EM. Cannabis, cannabidiol, and epilepsy—from receptors to clinical response. *Epilepsy Behav* 2014;41:277-282.
18. O'Shaughnessy WB. On the preparations of the Indian hemp, or Gunjah. *Prov Med J Retrospect Med Sci* 1843;5:363-369.
19. Reynolds JR. Epilepsy: its symptoms, treatment, and relation to other chronic convulsive diseases. J. Churchill (Ed.) London, 1861.
20. Gowers W. Epilepsy and other chronic convulsive disorders. Churchill (Ed.) London, 1881.
21. Gaoni Y, Mechoulam R. Isolation, structure, and partial synthesis of an active constituent of hashish. *J Am Chem Soc* 1964;86:1646-1647.
22. Gaoni Y, Mechoulam R. The isolation and structure of delta-1-tetrahydrocannabinol and other neutral cannabinoids from hashish. *J Am Chem Soc* 1971;93:217-224.
23. Adams R, Pease DC, Clark JH. Isolation of cannabinol, cannabidiol, and quebrachitol from red oil of Minnesota wild hemp. *J Am Chem Soc* 1940;62: 2194-2196.
24. Mechoulam R, Shvo Y, Hashish, I. The structure of cannabidiol. *Tetrahedron* 1963; 19:2073-2078.
25. Matsuda LA, et al. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* 1990;346:561-564.
26. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 1993;365:61-65.
27. Llano I, et al. Synaptic- and agonist-induced excitatory currents of Purkinje cells in rat cerebellar slices. *J Physiol* 1991;434:183-213.
28. Pitler TA, Alger BE. Postsynaptic spike firing reduces synaptic GABA_A responses in hippocampal pyramidal cells. *J Neurosci* 1992;12:4122-4132.
29. Kreitzer AC, Regehr WG. Retrograde inhibition of presynaptic calcium influx by endogenous cannabinoids at excitatory synapses onto Purkinje cells. *Neuron* 2001;29:717-727.
30. Kreitzer AC, Regehr WG. Cerebellar depolarization-induced suppression of inhibition is mediated by endogenous cannabinoids. *J Neurosci* 2001;21:RC174.
31. Wilson RI, Kunos G, Nicoll RA. Presynaptic specificity of endocannabinoid signaling in the hippocampus. *Neuron* 2001;31:453-462.
32. Devane WA, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 1992;258:1946-1949.
33. Mechoulam R, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem Pharmacol* 1995;50:83-90.
34. Sugiura T, et al. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochem Biophys Res Commun* 1995;215:89-97.
35. Alger BE. Retrograde signaling in the regulation of synaptic transmission: focus on endocannabinoids. *Prog Neurobiol* 2002;68:247-286.
36. Brown SP, Brenowitz SD, Regehr WG. Brief presynaptic bursts evoke synapse-specific retrograde inhibition mediated by endogenous cannabinoids. *Nat Neurosci* 2003;6:1048-1057.
37. Maejima T, Ohno-Shosaku T, Kano M. Endogenous cannabinoid as a retrograde messenger from depolarized postsynaptic neurons to presynaptic terminals. *Neurosci Res* 2001;40:205-210.
38. Melis M, et al. Prefrontal cortex stimulation induces 2-arachidonoyl-glycerol-mediated suppression of excitation in dopamine neurons. *J Neurosci* 2004;24:10707-10715.
39. Katona I, Freund TF. Endocannabinoid signaling as a synaptic circuit breaker in neurological disease. *Nat Med* 2008;14:923-930.
40. Di Marzo V, et al. Formation and inactivation of endogenous cannabinoid anandamide in central neurons. *Nature* 1994;372:686-691.
41. Di Marzo V, Deutsch DG. Biochemistry of the endogenous ligands of cannabinoid receptors. *Neurobiol Dis* 1998;5:386-404.
42. Di Marzo V, et al. Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action. *Trends Neurosci* 1998;21:521-528.
43. Sugiura T, et al. Biosynthesis and degradation of anandamide and 2-arachidonoylglycerol and their possible physiological significance. *Prostaglandins Leukot Essent Fatty Acids* 2002;66:173-192.
44. Stella N, Schweitzer P, Piomelli D. A second endogenous cannabinoid that modulates long-term potentiation. *Nature* 1997;388:773-778.
45. Pertwee RG. Cannabinoid receptor ligands: clinical and neuropharmacological considerations, relevant to future drug discovery and development. *Expert Opin Investig Drugs* 2000;9:1553-1571.
46. Pi-Sunyer F, et al. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients - RIO-North America: A randomized controlled trial. *JAMA* 2006;295:761-775.
47. Cahill K, Ussher M. Cannabinoid type 1 receptor antagonists (rimonabant) for smoking cessation. *Cochrane Database Syst Rev* 2007:CD005353.
48. Glass M., Felder CC. Concurrent stimulation of cannabinoid CB1 and dopamine D2 receptors augments cAMP accumulation in

- striatal neurons: evidence for a Gs linkage to the CB1 receptor. *J Neurosci* 1997;17:5327-5333.
49. Mackie K, Hille B. Cannabinoids inhibit N-type calcium channels in neuroblastoma-glioma cells. *Proc Natl Acad Sci U S A* 1992;89:3825-3829.
 50. Caulfield MP, Brown DA. Cannabinoid receptor agonists inhibit Ca current in NG108-15 neuroblastoma cells via a pertussis toxin-sensitive mechanism. *Br J Pharmacol* 1992;106:231-232.
 51. Twitchell W, Brown S, Mackie K. Cannabinoids inhibit N- and P/Q-type calcium channels in cultured rat hippocampal neurons. *J Neurophysiol* 1997;78:43-50.
 52. Szabo GG, et al. Presynaptic calcium channel inhibition underlies CB(1) cannabinoid receptor-mediated suppression of GABA release. *J Neurosci* 2014;34:7958-7963.
 53. Deadwyler SA, et al. Cannabinoids modulate potassium current in cultured hippocampal neurons. *Receptors Channels* 1993;1:121-134.
 54. Deadwyler SA, et al. Cannabinoids modulate voltage sensitive potassium A-current in hippocampal neurons via a cAMP-dependent process. *J Pharmacol Exp Ther* 1995;273:734-743.
 55. Hampson RE, et al. Role of cyclic AMP dependent protein kinase in cannabinoid receptor modulation of potassium "A-current" in cultured rat hippocampal neurons. *Life Sci* 1995;56:2081-2088.
 56. Mu J, et al. Protein kinase-dependent phosphorylation and cannabinoid receptor modulation of potassium A current (IA) in cultured rat hippocampal neurons. *Pflugers Arch* 2000;439:541-546.
 57. Henry DJ, Chavkin C. Activation of inwardly rectifying potassium channels (GIRK1) by co-expressed rat brain cannabinoid receptors in *Xenopus* oocytes. *Neurosci Lett* 1995;186:91-94.
 58. Mackie K, et al. Cannabinoids activate an inwardly rectifying potassium conductance and inhibit Q-type calcium currents in AtT20 cells transfected with rat brain cannabinoid receptor. *J Neurosci* 1995;15:6552-6561.
 59. McAllister SD, et al. Cannabinoid receptors can activate and inhibit G protein-coupled inwardly rectifying potassium channels in a *xenopus* oocyte expression system. *J Pharmacol Exp Ther* 1999;291:618-626.
 60. Photowala H, et al. G protein betagamma-subunits activated by serotonin mediate presynaptic inhibition by regulating vesicle fusion properties. *Proc Natl Acad Sci U S A* 2006;103:4281-4286.
 61. Schlicker E, Kathmann M. Modulation of transmitter release via presynaptic cannabinoid receptors. *Trends Pharmacol Sci* 2001;22:565-572.
 62. Chevalyere V, Takahashi KA, Castillo PE. Endocannabinoid-mediated synaptic plasticity in the CNS. *Annu Rev Neurosci* 2006;29:37-76.
 63. Piomelli D. The molecular logic of endocannabinoid signalling. *Nat Rev Neurosci* 2003;4:873-884.
 64. Katona I, et al. Presynaptically located CB1 cannabinoid receptors regulate GABA release from axon terminals of specific hippocampal interneurons. *J Neurosci* 1999; 19:4544-4558.
 65. Marsicano G, Lutz B. Expression of the cannabinoid receptor CB1 in distinct neuronal subpopulations in the adult mouse forebrain. *Eur J Neurosci* 1999;11: 4213-4225.
 66. Dudok B, et al. Cell-specific STORM super-resolution imaging reveals nanoscale organization of cannabinoid signaling. *Nat Neurosci* 2015;18:75-86.
 67. Kawamura Y, et al. The CB1 cannabinoid receptor is the major cannabinoid receptor at excitatory presynaptic sites in the hippocampus and cerebellum. *J Neurosci* 2006;26:2991-3001.
 68. Katona I, et al. Molecular composition of the endocannabinoid system at glutamatergic synapses. *J Neurosci* 2006;26:5628-5637.
 69. Lafourcade M, et al. Molecular components and functions of the endocannabinoid system in mouse prefrontal cortex. *PLoS One* 2007;2:e709.
 70. Wittmann G, et al. Distribution of type 1 cannabinoid receptor (CB1)-immunoreactive axons in the mouse hypothalamus. *J Comp Neurol* 2007;503:270-279.
 71. Robbe D, et al. Localization and mechanisms of action of cannabinoid receptors at the glutamatergic synapses of the mouse nucleus accumbens. *J Neurosci* 2001;21:109-116.
 72. Elsohly MA, Slade D. Chemical constituents of marijuana: the complex mixture of natural cannabinoids. *Life Sci* 2005;78:539-548.
 73. Joy JE. Marijuana and medicine: assessing the science base. National Academics Press, Washington, DC 1999.
 74. Huestis MA, et al. Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. *Arch Gen Psychiatry* 2001;58:322-328.
 75. Lichtman AH, Martin BR. Delta 9-tetrahydrocannabinol impairs spatial memory through a cannabinoid receptor mechanism. *Psychopharmacology (Berl)* 1996;126: 125-131.
 76. Mallet PE, Beninger RJ. The cannabinoid CB1 receptor antagonist SR141716A attenuates the memory impairment produced by delta 9-tetrahydrocannabinol or anandamide. *Psychopharmacology (Berl)* 1998;140:11-19.
 77. Varvel SA, et al. Differential effects of delta 9-THC on spatial reference and working memory in mice. *Psychopharmacology (Berl)* 2001;157:142-150.
 78. Da S, Takahashi RN. SR 141716A prevents delta 9-tetrahydrocannabinol-induced spatial learning deficit in a Morris-type water maze in mice. *Prog Neuropsychopharmacol Biol Psychiatry* 2002;26:321-325.
 79. Pagotto U, et al. The emerging role of the endocannabinoid system in endocrine regulation and energy balance. *Endocr Rev* 2006;27: 73-100.
 80. Abood ME, et al. Activation of the CB1 cannabinoid receptor protects cultured mouse spinal neurons against excitotoxicity. *Neurosci Lett* 2001;309:197-201.
 81. van der Stelt M, et al. Neuroprotection by Delta9-tetrahydrocannabinol, the main active compound in marijuana, against ouabain-induced in vivo excitotoxicity. *J Neurosci* 2001;21:6475-6479.
 82. El-Remessy AB, et al. Neuroprotective effect of (-)Delta9-tetrahydrocannabinol and cannabidiol in N-methyl-D-aspartate-induced retinal neurotoxicity: involvement of peroxynitrite. *Am J Pathol* 2003;163:1997-2008.
 83. Mechoulam R, Panikashvili D, Shohami E. Cannabinoids and brain injury: therapeutic implications. *Trends Mol Med* 2002;8: 58-61.
 84. Gilbert GL, et al. Delta9-tetrahydrocannabinol protects hippocampal neurons from excitotoxicity. *Brain Res* 2007;1128:61-69.
 85. Nagayama T, et al. Cannabinoids and neuroprotection in global and focal cerebral ischemia and in neuronal cultures. *J Neurosci* 1999;19:2987-2995.
 86. Zani A, et al. Delta9-tetrahydrocannabinol (THC) and AM 404 protect against cerebral ischaemia in gerbils through a mechanism involving cannabinoid and opioid receptors. *Br J Pharmacol* 2007;152:1301-1311.
 87. Hampson AJ, et al. Cannabidiol and (-)Delta9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc Natl Acad Sci U S A* 1998;95:8268-8273.
 88. Molina-Holgado F, Lledo A, Guaza C. Anandamide suppresses nitric oxide and TNF-alpha responses to Theiler's virus or endotoxin in astrocytes. *Neuroreport* 1997;8:1929-1933.
 89. Molina-Holgado F, et al. Role of CB1 and CB2 receptors in the inhibitory effects of cannabinoids on lipopolysaccharide-induced nitric oxide release in astrocyte cultures. *J Neurosci Res* 2002;67: 829-836.
 90. Shohami E, et al. Cytokine production in the brain following closed head injury: dexamethasone (HU-211) is a novel TNF-alpha

- inhibitor and an effective neuroprotectant. *J Neuroimmunol* 1997;72:169-177.
91. Puffenbarger RA, Boothe AC, Cabral GA. Cannabinoids inhibit LPS-inducible cytokine mRNA expression in rat microglial cells. *Glia* 2000;29:58-69.
 92. Cabral GA, Harmon KN, Carlisle SJ. Cannabinoid-mediated inhibition of inducible nitric oxide production by rat microglial cells: evidence for CB1 receptor participation. *Adv Exp Med Biol* 2001;493:207-214.
 93. Ehrhart J, et al. Stimulation of cannabinoid receptor 2 (CB2) suppresses microglial activation. *J Neuroinflammation* 2005;2:29.
 94. Klein TW, et al. The cannabinoid system and cytokine network. *Proc Soc Exp Biol Med* 2000;225:1-8.
 95. Molina-Holgado F, et al. Endogenous interleukin-1 receptor antagonist mediates anti-inflammatory and neuroprotective actions of cannabinoids in neurons and glia. *J Neurosci* 2003;23:6470-6474.
 96. Benito C, et al. Cannabinoid CB2 receptors in human brain inflammation. *Br J Pharmacol* 2008;153:277-285.
 97. De Petrocellis L, et al. Plant-derived cannabinoids modulate the activity of transient receptor potential channels of ankyrin type-1 and melastatin type-8. *J Pharmacol Exp Ther* 2008;325:1007-1015.
 98. De Petrocellis L, et al. Effects of cannabinoids and cannabinoid-enriched *Cannabis* extracts on TRP channels and endocannabinoid metabolic enzymes. *Br J Pharmacol* 2011;163:1479-1494.
 99. Qin N, et al. TRPV2 is activated by cannabidiol and mediates CGRP release in cultured rat dorsal root ganglion neurons. *J Neurosci* 2008;28:6231-6238.
 100. Vezzani A, et al. The role of inflammation in epilepsy. *Nat Rev Neurol* 2011;7:31-40.
 101. Walker L, Sills GJ. Inflammation and epilepsy: the foundations for a new therapeutic approach in epilepsy? *Epilepsy Curr* 2012;12:8-12.
 102. Devinsky O, et al. Glia and epilepsy: excitability and inflammation. *Trends Neurosci* 2013;36:174-184.
 103. Thomas BF, et al. Comparative receptor binding analyses of cannabinoid agonists and antagonists. *J Pharmacol Exp Ther* 1998;285:285-292.
 104. Bisogno T, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol* 2001;134:845-852.
 105. Pertwee RG. GPR55: a new member of the cannabinoid receptor clan? *Br J Pharmacol* 2007;152:984-986.
 106. Jones NA, et al. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. *J Pharmacol Exp Ther* 2010;332:569-577.
 107. Russo EB, et al. Agonistic properties of cannabidiol at 5-HT1a receptors. *Neurochem Res* 2005;30:1037-1043.
 108. Ahrens J, et al. The nonpsychotropic cannabinoid cannabidiol modulates and directly activates alpha-1 and alpha-1-Beta glycine receptor function. *Pharmacology* 2009;83:217-222.
 109. Ross HR, Napier I, Connor M. Inhibition of recombinant human T-type calcium channels by Delta9-tetrahydrocannabinol and cannabidiol. *J Biol Chem* 2008;283: 16124-16134.
 110. Drysdale AJ, et al. Cannabidiol-induced intracellular Ca²⁺ elevations in hippocampal cells. *Neuropharmacology* 2006;50:621-631.
 111. Ryan D, et al. Cannabidiol targets mitochondria to regulate intracellular Ca²⁺ levels. *J Neurosci* 2009;29:2053-2063.
 112. Rimmerman N, et al. The non-psychoactive plant cannabinoid, cannabidiol affects cholesterol metabolism-related genes in microglial cells. *Cell Mol Neurobiol* 2011; 31:921-930.
 113. Ross RA. The enigmatic pharmacology of GPR55. *Trends Pharmacol Sci* 2009;30: 156-163.
 114. Ryberg E, et al. The orphan receptor GPR55 is a novel cannabinoid receptor. *Br J Pharmacol* 2007;152:1092-1101.
 115. Lauckner JE, et al. GPR55 is a cannabinoid receptor that increases intracellular calcium and inhibits M current. *Proc Natl Acad Sci U S A* 2008;105:2699-2704.
 116. Oka S, et al. Identification of GPR55 as a lysophosphatidylinositol receptor. *Biochem Biophys Res Commun* 2007;362:928-934.
 117. Sylantsev S, et al. Cannabinoid- and lysophosphatidylinositol-sensitive receptor GPR55 boosts neurotransmitter release at central synapses. *Proc Natl Acad Sci U S A* 2013;110:5193-5198.
 118. Carrier EJ, Auchampach JA, Hillard CJ. Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. *Proc Natl Acad Sci U S A* 2006;103:7895-7900.
 119. Pandolfo P, et al. Cannabinoids inhibit the synaptic uptake of adenosine and dopamine in the rat and mouse striatum. *Eur J Pharmacol* 2011;655:38-45.
 120. Ferre S, et al. Adenosine-cannabinoid receptor interactions. Implications for striatal function. *Br J Pharmacol* 2010;160:443-453.
 121. De Petrocellis L, Di Marzo V. Non-CB1, non-CB2 receptors for endocannabinoids, plant cannabinoids, and synthetic cannabimimetics: focus on G-protein-coupled receptors and transient receptor potential channels. *J Neuroimmune Pharmacol* 2010;5:103-121.
 122. Booz GW. Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress. *Free Radic Biol Med* 2011;51:1054-1061.
 123. Hampson AJ, et al. Neuroprotective antioxidants from marijuana. *Ann N Y Acad Sci* 2000;899:274-282.
 124. Liou GI, et al. Mediation of cannabidiol anti-inflammation in the retina by equilibrative nucleoside transporter and A2A adenosine receptor. *Invest Ophthalmol Vis Sci* 2008;49:5526-5531.
 125. Hayakawa K, et al. Delayed treatment with cannabidiol has a cerebroprotective action via a cannabinoid receptor-independent myeloperoxidase-inhibiting mechanism. *J Neurochem* 2007;102: 1488-1496.
 126. Hayakawa K, et al. Therapeutic time window of cannabidiol treatment on delayed ischemic damage via high-mobility group box1-inhibiting mechanism. *Biol Pharm Bull* 2009;32:1538-1544.
 127. Iuvone T, et al. Neuroprotective effect of cannabidiol, a non-psychoactive component from *Cannabis sativa*, on beta-amyloid-induced toxicity in PC12 cells. *J Neurochem* 2004;89: 134-141.
 128. Esposito G, et al. Cannabidiol inhibits inducible nitric oxide synthase protein expression and nitric oxide production in beta-amyloid stimulated PC12 neurons through p38 MAP kinase and NF-kappaB involvement. *Neurosci Lett* 2006;399:91-95.
 129. Esposito G, et al. Cannabidiol in vivo blunts beta-amyloid induced neuroinflammation by suppressing IL-1beta and iNOS expression. *Br J Pharmacol* 2007;151:1272-1279.
 130. Pietr M, et al. Differential changes in GPR55 during microglial cell activation. *FEBS Lett* 2009;583:2071-2076.
 131. Staton PC, et al. The putative cannabinoid receptor GPR55 plays a role in mechanical hyperalgesia associated with inflammatory and neuropathic pain. *Pain* 2008;139: 225-236.
 132. Ben-Shabat S, et al. An entourage effect: inactive endogenous fatty acid glycerol esters enhance 2-arachidonoyl-glycerol cannabinoid activity. *Eur J Pharmacol* 1998;353: 23-31.
 133. Wagner H, Ulrich-Merzenich G. Synergy research: approaching a new generation of phytopharmaceuticals. *Phytomedicine* 2009;16:97-110.

134. Mechoulam R, Ben-Shabat S. From gan-zi-gun-nu to anandamide and 2-arachidonoylglycerol: the ongoing story of cannabis. *Nat Prod Rep* 1999;16:131-143.
135. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol* 2011;163:1344-1364.
136. Karniol IG, Carlini EA. Pharmacological interaction between cannabidiol and delta 9-tetrahydrocannabinol. *Psychopharmacologia* 1973;33:53-70.
137. Englund A, et al. Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. *J Psychopharmacol* 2013;27:19-27.
138. Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses* 2006;66:234-246.
139. Schubart CD, et al. Cannabis with high cannabidiol content is associated with fewer psychotic experiences. *Schizophr Res* 2011;130:216-221.
140. Hemaiswarya S, Kruthiventi AK, Doble M. Synergism between natural products and antibiotics against infectious diseases. *Phytomedicine* 2008;15:639-652.
141. Tallarida RJ. Quantitative methods for assessing drug synergism. *Genes Cancer* 2011; 2:1003-1008.
142. Hill AJ, et al. Phytocannabinoids as novel therapeutic agents in CNS disorders. *Pharmacol Ther* 2012;133:79-97.
143. Raol YH, Brooks-Kayal AR. Experimental models of seizures and epilepsies. *Prog Mol Biol Transl Sci* 2012;105:57-82.
144. Loscher W. Critical review of current animal models of seizures and epilepsy used in the discovery and development of new anti-epileptic drugs. *Seizure* 2011;20:359-368.
145. Simonato M, et al. The challenge and promise of anti-epileptic therapy development in animal models. *Lancet Neurol* 2014;13: 949-960.
146. Marsicano G, et al. CB1 cannabinoid receptors and on-demand defense against excitotoxicity. *Science* 2003;302:84-88.
147. Wallace MJ, et al. The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. *J Pharmacol Exp Ther* 2003;307: 129-137.
148. Karanian DA, et al. Endocannabinoid enhancement protects against kainic acid-induced seizures and associated brain damage. *J Pharmacol Exp Ther* 2007;322: 1059-1066.
149. Karanian DA, et al. Dual modulation of endocannabinoid transport and fatty acid amide hydrolase protects against excitotoxicity. *J Neurosci* 2005;25:7813-7820.
150. Naidoo V, et al. Equipotent inhibition of fatty acid amide hydrolase and monoacylglycerol lipase—dual targets of the endocannabinoid system to protect against seizure pathology. *Neurotherapeutics* 2012;9:801-813.
151. Deshpande LS, et al. Endocannabinoids block status epilepticus in cultured hippocampal neurons. *Eur J Pharmacol* 2007;558:52-59.
152. Monory K, et al. The endocannabinoid system controls key epileptogenic circuits in the hippocampus. *Neuron* 2006;51:455-466.
153. Guggenhuber S, et al. AAV vector-mediated overexpression of CB1 cannabinoid receptor in pyramidal neurons of the hippocampus protects against seizure-induced excitotoxicity. *PLoS One* 2010;5:e15707.
154. Alger BE. Seizing an opportunity for the endocannabinoid system. *Epilepsy Curr* 2014; 14:272-276.
155. Falenski KW, et al. Status epilepticus causes a long-lasting redistribution of hippocampal cannabinoid type 1 receptor expression and function in the rat pilocarpine model of acquired epilepsy. *Neuroscience* 2007;146:1232-1244.
156. Falenski KW, et al. Temporal characterization of changes in hippocampal cannabinoid CB(1) receptor expression following pilocarpine-induced status epilepticus. *Brain Res* 2009;1262:64-72.
157. Bhaskaran MD, Smith BN. Cannabinoid-mediated inhibition of recurrent excitatory circuitry in the dentate gyrus in a mouse model of temporal lobe epilepsy. *PLoS One* 2010;5:e10683.
158. Sayers KW, et al. Statistical parametric mapping reveals regional alterations in cannabinoid CB1 receptor distribution and G-protein activation in the 3D reconstructed epileptic rat brain. *Epilepsia* 2012;53:897-907.
159. Ludanyi A, et al. Downregulation of the CB1 cannabinoid receptor and related molecular elements of the endocannabinoid system in epileptic human hippocampus. *J Neurosci* 2008;28:2976-2990.
160. Romigi A, et al. Cerebrospinal fluid levels of the endocannabinoid anandamide are reduced in patients with untreated newly diagnosed temporal lobe epilepsy. *Epilepsia* 2010;51:768-772.
161. Wyeth MS, et al. Selective reduction of cholecystokinin-positive basket cell innervation in a model of temporal lobe epilepsy. *J Neurosci* 2010;30:8993-9006.
162. Sun C, et al. Loss of cholecystokinin-containing terminals in temporal lobe epilepsy. *Neurobiol Dis* 2014;62:44-55.
163. Karlocai MR, et al. Redistribution of CB1 cannabinoid receptors in the acute and chronic phases of pilocarpine-induced epilepsy. *PLoS One* 2011;6:e27196.
164. Magloczky Z, et al. Dynamic changes of CB1-receptor expression in hippocampi of epileptic mice and humans. *Epilepsia* 2010;51(Suppl. 3):115-120.
165. Chen K, et al. Long-term plasticity of endocannabinoid signaling induced by developmental febrile seizures. *Neuron* 2003;39:599-611.
166. Chen K, et al. Prevention of plasticity of endocannabinoid signaling inhibits persistent limbic hyperexcitability caused by developmental seizures. *J Neurosci* 2007;27: 46-58.
167. Hill AJ, Hill TD, Whalley B. The development of cannabinoid based therapies for epilepsy. In: Murillo-Rodriguez (Ed.) *Endocannabinoids: molecular, pharmacological, behavioral and clinical features*. bentham science publishers, Oak Park, IL, 2013, pp 164-204.
168. Manna SS, Umathe SN. Involvement of transient receptor potential vanilloid type 1 channels in the pro-convulsant effect of anandamide in pentylenetetrazole-induced seizures. *Epilepsy Res* 2012;100:113-124.
169. Luszczki JJ, et al. Arachidonyl-2'-chloroethylamide, a highly selective cannabinoid CB1 receptor agonist, enhances the anticonvulsant action of valproate in the mouse maximal electroshock-induced seizure model. *Eur J Pharmacol* 2006;547:65-74.
170. Luszczki JJ, et al. Effect of arachidonyl-2'-chloroethylamide, a selective cannabinoid CB1 receptor agonist, on the protective action of the various antiepileptic drugs in the mouse maximal electroshock-induced seizure model. *Prog Neuropsychopharmacol Biol Psychiatry* 2010;34:18-25.
171. Luszczki JJ, et al. Synthetic cannabinoid WIN 55,212-2 mesylate enhances the protective action of four classical antiepileptic drugs against maximal electroshock-induced seizures in mice. *Pharmacol Biochem Behav* 2011;98:261-267.
172. Luszczki JJ, et al. Effects of WIN 55,212-2 mesylate (a synthetic cannabinoid) on the protective action of clonazepam, ethosuximide, phenobarbital and valproate against pentylenetetrazole-induced clonic seizures in mice. *Prog Neuropsychopharmacol Biol Psychiatry* 2011;35:1870-1876.
173. Andres-Mach M, et al. Effect of ACEA—a selective cannabinoid CB1 receptor agonist on the protective action of different antiepileptic drugs in the mouse pentylenetetrazole-induced seizure model. *Prog Neuropsychopharmacol Biol Psychiatry* 2012;39: 301-309.
174. Luszczki JJ, et al. Effects of WIN 55,212-2 mesylate on the anticonvulsant action of lamotrigine, oxcarbazepine, pregabalin and topiramate against maximal electroshock-induced seizures in mice. *Eur J Pharmacol* 2013;720:247-254.

175. Florek-Luszczki M, et al. Effects of WIN 55,212-2 (a non-selective cannabinoid CB1 and CB 2 receptor agonist) on the protective action of various classical antiepileptic drugs in the mouse 6 Hz psychomotor seizure model. *J Neural Transm* 2014;121: 707-715.
176. Florek-Luszczki M, Zagaja M, Luszczki JJ. Influence of WIN 55, 212-2 on the anticonvulsant and acute neurotoxic potential of clobazam and lacosamide in the maximal electroshock-induced seizure model and chimney test in mice. *Epilepsy Res* 2014;108: 1728-1733.
177. Florek-Luszczki M, et al. Effects of WIN 55,212-2 (a synthetic cannabinoid CB1 and CB2 receptor agonist) on the anticonvulsant activity of various novel antiepileptic drugs against 6Hz-induced psychomotor seizures in mice. *Pharmacol Biochem Behav* 2015; 130:53-58.
178. Chesher GB, Jackson DM. The effect of withdrawal from cannabis on pentylenetetrazol convulsive threshold in mice. *Psychopharmacologia* 1974;40: 129-135.
179. Chesher GB, Jackson DM, Malor RM. Interaction of delta9-tetrahydrocannabinol and cannabidiol with phenobarbitone in protecting mice from electrically induced convulsions. *J Pharm Pharmacol* 1975;27:608-609.
180. National Toxicology Program. NTP toxicology and carcinogenesis studies of 1-trans-delta(9)-tetrahydrocannabinol (CAS No. 1972-08-3) in F344 rats and B6C3F1 mice (gavage studies). *Natl Toxicol Program Tech Rep Ser* 1996;446:1-317.
181. Hill AJ, et al. Cannabidiol is anticonvulsant in mouse and rat. *Br J Pharmacol* 2012;167:1629-1642.
182. Oviedo A, Glowa J, Herkenham M. Chronic cannabinoid administration alters cannabinoid receptor binding in rat brain: a quantitative autoradiographic study. *Brain Res* 1993;616:293-302.
183. Rodriguez de Fonseca F, et al. Downregulation of rat brain cannabinoid binding sites after chronic delta 9-tetrahydrocannabinol treatment. *Pharmacol Biochem Behav* 1994;47:33-40.
184. Sim LJ, et al. Effects of chronic treatment with delta9-tetrahydrocannabinol on cannabinoid-stimulated [35S]GTPgammaS autoradiography in rat brain. *J Neurosci* 1996;16:8057-8066.
185. Fan F, et al. Cannabinoid receptor down-regulation without alteration of the inhibitory effect of CP 55,940 on adenylyl cyclase in the cerebellum of CP 55,940-tolerant mice. *Brain Res* 1996;706: 13-20.
186. Romero J, et al. Effects of chronic exposure to delta9-tetrahydrocannabinol on cannabinoid receptor binding and mRNA levels in several rat brain regions. *Brain Res Mol Brain Res* 1997;46:100-108.
187. Romero J, et al. Autoradiographic analysis of cannabinoid receptor binding and cannabinoid agonist-stimulated [35S]GTP gamma S binding in morphine-dependent mice. *Drug Alcohol Depend* 1998;50:241-249.
188. Romero J, et al. Cannabinoid receptor and WIN-55,212-2-stimulated [35S]GTP gamma S binding and cannabinoid receptor mRNA levels in the basal ganglia and the cerebellum of adult male rats chronically exposed to delta 9-tetrahydrocannabinol. *J Mol Neurosci* 1998;11:109-119.
189. Romero J, et al. Time-course of the cannabinoid receptor down-regulation in the adult rat brain caused by repeated exposure to delta9-tetrahydrocannabinol. *Synapse* 1998;30:298-308.
190. Zhuang S, et al. Effects of long-term exposure to delta9-THC on expression of cannabinoid receptor (CB1) mRNA in different rat brain regions. *Brain Res Mol Brain Res* 1998;62:141-149.
191. Hsieh C, et al. Internalization and recycling of the CB1 cannabinoid receptor. *J Neurochem* 1999;73:493-501.
192. Corchero J, et al. Time-dependent differences of repeated administration with Delta9-tetrahydrocannabinol in proenkephalin and cannabinoid receptor gene expression and G-protein activation by mu-opioid and CB1-cannabinoid receptors in the caudateputamen. *Brain Res Mol Brain Res* 1999;67:148-157.
193. Breivogel CS, et al. Chronic delta9-tetrahydrocannabinol treatment produces a time-dependent loss of cannabinoid receptors and cannabinoid receptor-activated G proteins in rat brain. *J Neurochem* 1999;73:2447-2459.
194. Breivogel CS, et al. The effects of delta9-tetrahydrocannabinol physical dependence on brain cannabinoid receptors. *Eur J Pharmacol* 2003;459:139-150.
195. McKinney DL, et al. Dose-related differences in the regional pattern of cannabinoid receptor adaptation and in vivo tolerance development to delta9-tetrahydrocannabinol. *J Pharmacol Exp Ther* 2008;324:664-673.
196. Sim-Selley LJ, Martin BR. Effect of chronic administration of R-(+)-[2,3-Dihydro-5-methyl-3-[(morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazinyl]-(1-naphthalenyl)methanone mesylate (WIN55,212-2) or delta(9)-tetrahydrocannabinol on cannabinoid receptor adaptation in mice. *J Pharmacol Exp Ther* 2002;303:36-44.
197. Sim-Selley LJ. Regulation of cannabinoid CB1 receptors in the central nervous system by chronic cannabinoids. *Crit Rev Neurobiol* 2003;15:91-119.
198. Sim-Selley LJ, et al. Prolonged recovery rate of CB1 receptor adaptation after cessation of long-term cannabinoid administration. *Mol Pharmacol* 2006;70:986-996.
199. Martin BR, Sim-Selley LJ, Selley DE. Signaling pathways involved in the development of cannabinoid tolerance. *Trends Pharmacol Sci* 2004;25:325-330.
200. Villares J. Chronic use of marijuana decreases cannabinoid receptor binding and mRNA expression in the human brain. *Neuroscience* 2007;145:323-334.
201. Coutts AA, et al. Agonist-induced internalization and trafficking of cannabinoid CB1 receptors in hippocampal neurons. *J Neurosci* 2001;21:2425-2433.
202. Lundberg DJ, Daniel AR, Thayer SA. Delta(9)-Tetrahydrocannabinol-induced desensitization of cannabinoid-mediated inhibition of synaptic transmission between hippocampal neurons in culture. *Neuropharmacology* 2005;49:1170-1177.
203. Deshpande LS, Blair RE, DeLorenzo RJ. Prolonged cannabinoid exposure alters GABA(A) receptor mediated synaptic function in cultured hippocampal neurons. *Exp Neurol* 2011;229:264-273.
204. Dewey WL. Cannabinoid pharmacology. *Pharmacol Rev* 1986;38:151-178.
205. Abood ME, et al. Development of behavioral tolerance to delta 9-THC without alteration of cannabinoid receptor binding or mRNA levels in whole brain. *Pharmacol Biochem Behav* 1993;46:575-579.
206. Ten Ham M, Loskota WJ, Lomax P. Acute and chronic effects of beta9-tetrahydrocannabinol on seizures in the gerbil. *Eur J Pharmacol* 1975;31:148-152.
207. Corcoran ME, McCaughan JA, Jr., Wada JA. Antiepileptic and prophylactic effects of tetrahydrocannabinols in amygdaloid kindled rats. *Epilepsia* 1978;19: 47-55.
208. Colasanti BK, Lindamood C, 3rd, Craig CR. Effects of marijuana cannabinoids on seizure activity in cobalt-epileptic rats. *Pharmacol Biochem Behav* 1982;16: 573-578.
209. Karler R, Turkianis SA. Subacute cannabinoid treatment: anticonvulsant activity and withdrawal excitability in mice. *Br J Pharmacol* 1980;68:479-484.
210. Blair RE, et al. Prolonged exposure to WIN55,212-2 causes down-regulation of the CB1 receptor and the development of tolerance to its anticonvulsant effects in the hippocampal neuronal culture model of acquired epilepsy. *Neuropharmacology* 2009;57:208-218.
211. Jones RT, Benowitz N, Bachman J. Clinical studies of cannabis tolerance and dependence. *Ann N Y Acad Sci* 1976;282:221-239.

212. Jones RT, Benowitz NL, Herning RI. Clinical relevance of cannabis tolerance and dependence. *J Clin Pharmacol* 1981;21(8-9 Suppl.):143S-152S.
213. Kirk JM, de Wit H. Responses to oral delta9-tetrahydrocannabinol in frequent and infrequent marijuana users. *Pharmacol Biochem Behav* 1999;63:137-142.
214. Hart CL, et al. Comparison of smoked marijuana and oral Delta(9)-tetrahydrocannabinol in humans. *Psychopharmacology (Berl)* 2002;164:407-415.
215. Babor TF, et al. Marijuana consumption and tolerance to physiological and subjective effects. *Arch Gen Psychiatry* 1975;32:1548-1552.
216. Nowlan R, Cohen S. Tolerance to marijuana: heart rate and subjective "high". *Clin Pharmacol Ther* 1977;22:550-556.
217. Aceto MD, et al. Cannabinoid precipitated withdrawal by the selective cannabinoid receptor antagonist, SR 141716A. *Eur J Pharmacol* 1995;282:R1-R2.
218. Tsou K, Patrick SL, Walker JM. Physical withdrawal in rats tolerant to delta 9-tetrahydrocannabinol precipitated by a cannabinoid receptor antagonist. *Eur J Pharmacol* 1995;280:R13-R15.
219. Rodriguez de Fonseca F, et al. Activation of corticotropin-releasing factor in the limbic system during cannabinoid withdrawal. *Science* 1997;276:2050-2054.
220. Kaymakcalan S. Tolerance to and dependence on cannabis. *Bull Narc* 1973;25:39-47.
221. Beardsley PM, Balster RL, Harris LS. Dependence on tetrahydrocannabinol in rhesus monkeys. *J Pharmacol Exp Ther* 1986;239:311-319.
222. Budney AJ, Hughes JR. The cannabis withdrawal syndrome. *Curr Opin Psychiatry* 2006;19:233-238.
223. Karler R, et al. Interaction between delta-9-tetrahydrocannabinol and kindling by electrical and chemical stimuli in mice. *Neuropharmacology* 1984;23:1315-1320.
224. Karler R, Calder LD, Turkanis SA. Prolonged CNS hyperexcitability in mice after a single exposure to delta-9-tetrahydrocannabinol. *Neuropharmacology* 1986;25:441-446.
225. Hegde M, et al. Seizure exacerbation in two patients with focal epilepsy following marijuana cessation. *Epilepsy Behav* 2012;25:563-566.
226. Ellison JM, Gelwan E, Ogletree J. Complex partial seizure symptoms affected by marijuana abuse. *J Clin Psychiatry* 1990;51:439-440.
227. Leite JR, Carlini EA. Failure to obtain "cannabis-directed behavior" and abstinence syndrome in rats chronically treated with cannabis sativa extracts. *Psychopharmacologia* 1974;36:133-145.
228. Robson P. Abuse potential and psychoactive effects of delta-9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine. *Expert Opin Drug Saf* 2011;10:675-685.
229. Wade DT, et al. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler* 2004;10:434-441.
230. Russo EB, Guy GW, Robson PJ. Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. *Chem Biodivers* 2007; 4:1729-1743.
231. Rog DJ, Nurmikko TJ, Young CA. Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. *Clin Ther* 2007;29: 2068-2079.
232. Perez J. Combined cannabinoid therapy via an oromucosal spray. *Drugs Today (Barc)* 2006;42:495-503.
233. Crippa JA, et al. Cannabidiol for the treatment of cannabis withdrawal syndrome: a case report. *J Clin Pharm Ther* 2013;38:162-164.
234. Allsop DJ, et al. Nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. *JAMA Psychiatry* 2014;71:281-291.
235. Allsop DJ, Lintzeris N, Copeland J, Dunlop A, McGregor IS. Cannabinoid replacement therapy (CRT): Nabiximols (Sativex) as a novel treatment for cannabis withdrawal. *Clin Pharmacol Ther* 2015;97:571-574.
236. Keeler MH, Reifler CB. Grand mal convulsions subsequent to marijuana use. Case report. *Dis Nerv Syst* 1967;28:474-475.
237. Lapoint J, et al. Severe toxicity following synthetic cannabinoid ingestion. *Clin Toxicol (Phila)* 2011;49:760-764.
238. Jinwala FN, Gupta M. Synthetic cannabis and respiratory depression. *J Child Adolesc Psychopharmacol* 2012;22:459-462.
239. Hermanns-Clausen M, et al. Acute intoxication by synthetic cannabinoids—four case reports. *Drug Test Anal* 2013;5:790-794.
240. Hermanns-Clausen M, et al. Acute toxicity due to the confirmed consumption of synthetic cannabinoids: clinical and laboratory findings. *Addiction* 2013;108: 534-544.
241. McQuade D, et al. First European case of convulsions related to analytically confirmed use of the synthetic cannabinoid receptor agonist AM-2201. *Eur J Clin Pharmacol* 2013; 69:373-376.
242. Pant S, et al. Spicy seizure. *Am J Med Sci* 2012;344:67-68.
243. Tofighi B, Lee JD. Internet highs—seizures after consumption of synthetic cannabinoids purchased online. *J Addict Med* 2012;6: 240-241.
244. de Havenon A, et al. The secret "spice": an undetectable toxic cause of seizure. *Neurohospitalist* 2011;1:182-186.
245. Castaneto MS, et al. Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. *Drug Alcohol Depend* 2014;144:12-41.
246. Davis JP, Ramsey HH. Anti-epileptic action of marijuana-active substances. *Fed Proc Am Soc Exp Biol* 1949;8:284.
247. Consroe PF, Wood GC, Buchsbaum H. Anticonvulsant nature of marihuana smoking. *JAMA* 1975;234:306-307.
248. Lorenz R. On the application of cannabis in paediatrics and epileptology. *Neuro Endocrinol Lett* 2004;25:40-44.
249. Mortati K, Dworetzky B, Devinsky O. Marijuana: an effective antiepileptic treatment in partial epilepsy? A case report and review of the literature. *Rev Neurol Dis* 2007;4:103-106.
250. Gordon E, Devinsky O. Alcohol and marijuana: effects on epilepsy and use by patients with epilepsy. *Epilepsia* 2001;42:1266-1272.
251. Maa E, Figi P. The case for medical marijuana in epilepsy. *Epilepsia* 2014;55: 783-786.
252. Corral VJ. Differential effects of medical marijuana based on strain and route of administration: a three-year observational study. *J Cannabis Ther* 2001;1:43-59.
253. Hamerle M, et al. Cannabis and other illicit drug use in epilepsy patients. *Eur J Neurol*, 2014;21:167-170.
254. Gieringer D. Medical use of cannabis: experience in California. Haworth Press, Binghamton, NY, 2001.
255. Feeny D, Spiker M. Marijuana and epilepsy: activation of symptoms by delta-9-THC. In: C.S and S.R.C (Eds.). The therapeutic potential of marihuana. Plenum Press, New York, 1976.
256. Alldredge BK, Lowenstein DH, Simon RP. Seizures associated with recreational drug abuse. *Neurology* 1989;39:1037-1039.
257. Brust JC, et al. Marijuana use and the risk of new onset seizures. *Trans Am Clin Climatol Assoc* 1992;103:176-181.
258. Gross DW, et al. Marijuana use and epilepsy: prevalence in patients of a tertiary care epilepsy center. *Neurology* 2004;62:2095-2097.
259. Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy Behav* 2013;29:574-577.

260. Press CA, Knupp KG, Chapman KE. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. *Epilepsy Behav* 2015;45: 49–52.
261. Mechoulam R, Carlini EA. Toward drugs derived from cannabis. *Naturwissenschaften* 1978;65:174–179.
262. Cunha JM, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology* 1980;21:175–185.
263. Ames FR, Cridland S. Anticonvulsant effect of cannabidiol. *S Afr Med J* 1986; 69:14.
264. Tremblay B, Sherman M. Double-blind clinical study of cannabidiol as a secondary anticonvulsant. In: *Marijuana '90 international conference on cannabis and cannabinoids*, Kolympari, Crete, 1990.
265. van Rijckevorsel K. Treatment of Lennox-Gastaut syndrome: overview and recent findings. *Neuropsychiatr Dis Treat* 2008;4: 1001–1019.
266. Dravet C. The core Dravet syndrome phenotype. *Epilepsia* 2011;52(Suppl. 2):3–9.
267. Mathern GW, Beninsig L, Nehlig A. Fewer specialists support using medical marijuana and CBD in treating epilepsy patients compared with other medical professionals and patients: result of Epilepsia's survey. *Epilepsia* 2015;56:1–6.
268. Volkow ND, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med* 2014;371:879.
269. Morales-Munoz I, et al. Characterizing cannabis-induced psychosis: a study with prepulse inhibition of the startle reflex. *Psychiatry Res* 2014;220:535–540.
270. Lynskey M, Hall W. The effects of adolescent cannabis use on educational attainment: a review. *Addiction* 2000;95:1621–1630.
271. Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. *J Addict Med* 2011;5: 1–8.
272. Lisdahl KM, et al. Dare to delay? The impacts of adolescent alcohol and marijuana use onset on cognition, brain structure, and function. *Front Psychiatry* 2013;4:53.
273. Crane NA, Schuster RM, Gonzalez R. Preliminary evidence for a sex-specific relationship between amount of cannabis use and neurocognitive performance in young adult cannabis users. *J Int Neuropsychol Soc* 2013;19:1009–1015.
274. Jacobus J, et al. Cortical thickness and neurocognition in adolescent marijuana and alcohol users following 28 days of monitored abstinence. *J Stud Alcohol Drugs* 2014; 75:729–743.
275. Gilman JM, et al. Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users. *J Neurosci* 2014;34: 5529–5538.
276. Gruber SA, et al. Worth the wait: effects of age of onset of marijuana use on white matter and impulsivity. *Psychopharmacology (Berl)* 2014;231:1455–1465.
277. Tortoriello G, et al. Miswiring the brain: Delta9-tetrahydrocannabinol disrupts cortical development by inducing an SCG10/stathmin-2 degradation pathway. *EMBO J* 2014;33: 668–685.
278. Raver SM, Haughwout SP, Keller A. Adolescent cannabinoid exposure permanently suppresses cortical oscillations in adult mice. *Neuropsychopharmacology* 2013;38:2338–2347.
279. Raver SM, Keller A. Permanent suppression of cortical oscillations in mice after adolescent exposure to cannabinoids: receptor mechanisms. *Neuropharmacology* 2014;86:161–173.
280. Houck JM, Bryan AD, Feldstein Ewing SW. Functional connectivity and cannabis use in high-risk adolescents. *Am J Drug Alcohol Abuse* 2013;39:414–423.
281. Pavisian B, et al. Effects of cannabis on cognition in patients with MS: a psychometric and MRI study. *Neurology* 2014;82:1879–1887.
282. Guy GW, Robson PJ. A phase I, open label, four-way crossover study to compare the pharmacokinetic profiles of a single dose of 20 mg of a cannabis based medicine extract (CBME) administered on 3 different areas of the buccal mucosa and to investigate the pharmacokinetics of CBME per oral in healthy male and female volunteers (GWPK0112). *J Cannabis Ther* 2003;3:79–120.
283. Hawksworth G, McArdle K. *Metabolism and pharmacokinetics of cannabinoids*. Pharmaceutical Press, London, 2004.
284. Bornheim LM, et al. Characterization of cannabidiol-mediated cytochrome P450 inactivation. *Biochem Pharmacol* 1993;45: 1323–1331.
285. Yamaori S, et al. Cannabidiol, a major phytocannabinoid, as a potent atypical inhibitor for CYP2D6. *Drug Metab Dispos* 2011;39:2049–2056.
286. Jiang R, et al. Identification of cytochrome P450 enzymes responsible for metabolism of cannabidiol by human liver microsomes. *Life Sci* 2011;89:165–170.
287. Yamaori S, et al. Potent inhibition of human cytochrome P450 3A isoforms by cannabidiol: role of phenolic hydroxyl groups in the resorcinol moiety. *Life Sci* 2011;88:730–736.
288. Jiang R, et al. Cannabidiol is a potent inhibitor of the catalytic activity of cytochrome P450 2C19. *Drug Metab Pharmacokin* 2013;28:332–338.
289. Stout SM, Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. *Drug Metab Rev* 2014;46:86–95.
290. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: interactions between antiepileptic drugs and other drugs. *Lancet Neurol* 2003;2: 473–481.
291. Yamaori S, et al. Characterization of major phytocannabinoids, cannabidiol and cannabinol, as isoform-selective and potent inhibitors of human CYP1 enzymes. *Biochem Pharmacol* 2010;79: 1691–1698.
292. Friedman D, et al. The effect of Epidiolex (Cannabidiol) on serum levels of concomitant anti-epileptic drugs in children and young adults with treatment-resistant epilepsy in an expanded access program. In: *American Epilepsy Society*, Seattle, WA, 2014.
293. Espay AJ, et al. Placebo effect of medication cost in Parkinson disease: a randomized double-blind study. *Neurology* 2015;84: 794–802.
294. Weimer K, et al. Placebo effects in children: a review. *Pediatr Res* 2013;74:96–102.
295. Kemeny ME, et al. Placebo response in asthma: a robust and objective phenomenon. *J Allergy Clin Immunol* 2007;119:1375–1381.
296. Rheims S, et al. Greater response to placebo in children than in adults: a systematic review and meta-analysis in drug-resistant partial epilepsy. *PLoS Med* 2008;5: e166.
297. Anon. Double-blind, placebo-controlled evaluation of cinromide in patients with the Lennox-Gastaut Syndrome. The Group for the Evaluation of Cinromide in the Lennox-Gastaut Syndrome. *Epilepsia* 1989;30:422–429.
298. Rekan T. THC:CBD spray and MS spasticity symptoms: data from latest studies. *Eur Neurol* 2014;71(Suppl. 1):4–9.
299. Naderi N, et al. Evaluation of interactions between cannabinoid compounds and diazepam in electroshock-induced seizure model in mice. *J Neural Transm* 2008;115:1501–1511.
300. Naderi N, et al. Modulation of anticonvulsant effects of cannabinoid compounds by GABA-A receptor agonist in acute pentylenetetrazole model of seizure in rat. *Neurochem Res* 2011;36:1520–1525.
301. Vilela LR, et al. Effects of cannabinoids and endocannabinoid hydrolysis inhibition on pentylenetetrazole-induced seizure and electroencephalographic activity in rats. *Epilepsy Res* 2013;104: 195–202.

302. Shubina L, Aliev R, Kitchigina V. Attenuation of kainic acid-induced status epilepticus by inhibition of endocannabinoid transport and degradation in guinea pigs. *Epilepsy Res* 2015;111:33-44.
303. Wendt H, et al. Targeting the endocannabinoid system in the amygdala kindling model of temporal lobe epilepsy in mice. *Epilepsia* 2011;52:e62-e65.
304. Wallace MJ, et al. Assessment of the role of CB1 receptors in cannabinoid anticonvulsant effects. *Eur J Pharmacol* 2001;428:51-57.
305. Payandemehr B, et al. Involvement of PPAR receptors in the anticonvulsant effects of a cannabinoid agonist, WIN 55,212-2. *Prog Neuropsychopharmacol Biol Psychiatry* 2015;57:140-145.
306. van Rijn CM, et al. WAG/Rij rats show a reduced expression of CB(1) receptors in thalamic nuclei and respond to the CB(1) receptor agonist, R(+)-WIN55,212-2, with a reduced incidence of spike-wave discharges. *Epilepsia* 2010;51:1511-1521.
307. Citraro R, et al. CB1 agonists, locally applied to the corticothalamic circuit of rats with genetic absence epilepsy, reduce epileptic manifestations. *Epilepsy Res* 2013; 106:74-82.
308. Lambert DM, et al. Anticonvulsant activity of N-palmitoylethanolamide, a putative endocannabinoid, in mice. *Epilepsia* 2001;42:321-327.
309. Sheerin AH, et al. Selective antiepileptic effects of N-palmitoylethanolamide, a putative endocannabinoid. *Epilepsia* 2004;45:1184-1188.
310. Wallace MJ, Martin BR, DeLorenzo RJ. Evidence for a physiological role of endocannabinoids in the modulation of seizure threshold and severity. *Eur J Pharmacol* 2002;452:295-301.
311. Shafaroodi H, et al. The interaction of cannabinoids and opioids on pentylenetetrazole-induced seizure threshold in mice. *Neuropharmacology* 2004;47:390-400.
312. Bahremand A, et al. The cannabinoid anticonvulsant effect on pentylenetetrazole-induced seizure is potentiated by ultra-low dose naltrexone in mice. *Epilepsy Res* 2008;81:44-51.
313. Bahremand A, et al. Involvement of nitergic system in the anticonvulsant effect of the cannabinoid CB(1) agonist ACEA in the pentylenetetrazole-induced seizure in mice. *Epilepsy Res* 2009;84:110-119.
314. Rudenko V, et al. Inverse relationship of cannabimimetic (R+)WIN 55, 212 on behavior and seizure threshold during the juvenile period. *Pharmacol Biochem Behav* 2012;100:474-484.
315. Di Maio R, Cannon JR, Timothy Greenamyre J. Post-status epilepticus treatment with the cannabinoid agonist WIN 55,212-2 prevents chronic epileptic hippocampal damage in rats. *Neurobiol Dis* 2014;73C:356-365.
316. Rizzo V, et al. Evidences of cannabinoids-induced modulation of paroxysmal events in an experimental model of partial epilepsy in the rat. *Neurosci Lett* 2009;462:135-139.
317. Kow RL, et al. Modulation of pilocarpine-induced seizures by cannabinoid receptor 1. *PLoS One* 2014;9:e95922.
318. Kozan R, Ayyildiz M, Agar E. The effects of intracerebroventricular AM-251, a CB1-receptor antagonist, and ACEA, a CB1-receptor agonist, on penicillin-induced epileptiform activity in rats. *Epilepsia* 2009;50:1760-1767.
319. Cakil D, et al. The effect of co-administration of the NMDA blocker with agonist and antagonist of CB1-receptor on penicillin-induced epileptiform activity in rats. *Epilepsy Res* 2011;93:128-137.
320. van Rijn CM, et al. Endocannabinoid system protects against cryptogenic seizures. *Pharmacol Rep* 2011;63:165-168.
321. Vinogradova LV, Shatskova AB, van Rijn CM. Pro-epileptic effects of the cannabinoid receptor antagonist SR141716 in a model of audiogenic epilepsy. *Epilepsy Res* 2011;96:250-256.
322. Gholizadeh S, et al. Ultra-low dose cannabinoid antagonist AM251 enhances cannabinoid anticonvulsant effects in the pentylenetetrazole-induced seizure in mice. *Neuropharmacology* 2007;53:763-770.
323. Dudek FE, et al. The effect of the cannabinoid-receptor antagonist, SR141716, on the early stage of kainate-induced epileptogenesis in the adult rat. *Epilepsia* 2010;51(Suppl. 3):126-130.
324. Echegoyen J, et al. Single application of a CB1 receptor antagonist rapidly following head injury prevents long-term hyperexcitability in a rat model. *Epilepsy Res* 2009;85:123-127.
325. Sofia RD, Kubena RK, Barry, H, 3rd. Comparison among four vehicles and four routes for administering delta9-tetrahydrocannabinol. *J Pharm Sci* 1974;63:939-941.
326. Chesher GB, Jackson DM. Anticonvulsant effects of cannabinoids in mice: drug interactions within cannabinoids and cannabinoid interactions with phenytoin. *Psychopharmacologia* 1974;37:255-264.
327. Johnson DD, et al. Epileptiform seizures in domestic fowl. V. The anticonvulsant activity of delta9-tetrahydrocannabinol. *Can J Physiol Pharmacol* 1975;53:1007-1013.
328. Wada JA, Osawa T, Corcoran ME. Effects of tetrahydrocannabinols on kindled amygdaloid seizures and photogenic seizures in Senegalese baboons, *Papio papio*. *Epilepsia* 1975;16:439-448.
329. Boggan WO, Steele RA, Freedman DX. 9-Tetrahydrocannabinol effect on audiogenic seizure susceptibility. *Psychopharmacologia* 1973;29:101-106.
330. Corcoran ME, McCaughran JA, Jr., Wada JA. Acute antiepileptic effects of 9-tetrahydrocannabinol in rats with kindled seizures. *Exp Neurol* 1973;40:471-483.
331. Wada JA, et al. Antiepileptic and prophylactic effects of tetrahydrocannabinols in amygdaloid kindled cats. *Epilepsia* 1975;16:503-510.
332. Turkanis SA, et al. An electrophysiological analysis of the anticonvulsant action of cannabidiol on limbic seizures in conscious rats. *Epilepsia* 1979;20:351-363.
333. Izquierdo I, Orsingher OA, Berardi AC. Effect of cannabidiol and of other cannabis sativa compounds on hippocampal seizure discharges. *Psychopharmacologia* 1973;28:95-102.
334. Karler R, Turkanis SA. Cannabis and epilepsy. *Adv Biosci* 1978;22-23:619-641.
335. Consroe P, et al. Effects of cannabidiol on behavioral seizures caused by convulsant drugs or current in mice. *Eur J Pharmacol* 1982;83:293-298.
336. Shirazi-zand Z, et al. The role of potassium BK channels in anticonvulsant effect of cannabidiol in pentylenetetrazole and maximal electroshock models of seizure in mice. *Epilepsy Behav* 2013;28:1-7.
337. Hill TD, et al. Cannabidiol-rich cannabis extracts are anticonvulsant in mouse and rat via a CB1 receptor-independent mechanism. *Br J Pharmacol* 2013;170:679-692.
338. Jones NA, et al. Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures. *Seizure* 2012;21:344-352.

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William D. Troutt N.M.D.^a & Matthew D. DiDonato Ph.D.^a

^a Medical Marijuana Research Institute, Mesa, AZ

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Medical Cannabis in Arizona: Patient Characteristics, Perceptions, and Impressions of Medical Cannabis Legalization

William D. Troutt, N.M.D. & Matthew D. DiDonato, Ph.D.

Abstract—Many advances have been made toward understanding the benefits of medical cannabis. However, less is known about medical cannabis patients themselves. Prior research has uncovered many important patient characteristics, but most of that work has been conducted with participants in California, who may not represent medical cannabis patients throughout the United States. Furthermore, it is unknown if medical cannabis legalization, which typically imposes strict regulations on cannabis cultivation and sale, impacts patients' experiences acquiring and using cannabis. The goal of this study was to address these limitations by (1) examining the characteristics, perceptions, and behaviors of medical cannabis patients in Arizona; and (2) questioning participants with a history of cannabis use regarding their experiences with cannabis before and after legalization. Patients in Arizona share many characteristics with those in California, but also key differences, such as average age and degree of cannabis consumption. Participants also had positive perceptions of the effect of medical cannabis legalization, reporting that feelings of safety and awareness were higher after legalization compared to before. The results are discussed in relation to evidence from patients in other states and in terms of their potential policy implications.

Keywords—Arizona, medical cannabis, medical cannabis legalization, patient characteristics, perceptions

Support for the use of cannabis for medical purposes is growing throughout the United States. To date, 23 states and the District of Columbia have enacted laws legalizing medical cannabis, and 16 states have similar legislation under consideration. Recent polls also show that the majority of Americans believe that cannabis should be legalized for medical purposes (Anderson Robbins Research & Shaw & Company Research 2013; Associated Press-CNBC 2010), and the popularity of this sentiment has

increased over time (Anderson Robbins Research & Shaw & Company Research 2013).

Support may be on the rise, in part, due to research that shows the potential therapeutic effects of medical cannabis. Animal studies, for example, show that cannabis-derived extracts mitigate cancer cell proliferation and tumor growth (Aviello et al. 2012) and have antidepressant-like effects (Jiang et al. 2005). Studies also show that cannabis may be beneficial for humans. Bar-Sela and colleagues (2013) found that nausea, vomiting, weight loss, sleep disorders, and pain were reduced in cancer patients after 6–8 weeks of cannabis use. Studies also show that cannabis significantly reduces chronic pain (see Lynch and Campbell 2011),

Medical Marijuana Research Institute, Mesa, AZ.

Please address correspondence to William D. Troutt, 10613 N. Hayden Rd., Suite J-107, Scottsdale, AZ 85260; phone: +1-480-948-2008; email: dtroutt@yahoo.com

inflammatory bowel disease (Allegretti et al. 2013), post-traumatic stress disorder (Greer, Grob, and Halberstadt 2014), and seizure disorders (Lorenz 2004).

Although many advances have been made in understanding the benefits of medical cannabis, less is known about US medical cannabis patients themselves. Demographically, most patients are White, male, and approximately 35 to 45 years of age (Bonn-Miller et al. 2014; Grella, Rodriguez, and Kim 2014; Ryan-Ibarra, Induni, and Ewing 2015; Aggarwal et al. 2013; Ilgen et al. 2013; Nunberg et al. 2011; Reinerman et al. 2011; Aggarwal et al. 2009; Reiman 2009; O'Connell and Bou-Matar 2007; Harris et al. 2000). Most patients report medicating with cannabis daily (Bonn-Miller et al. 2014; Ilgen et al. 2013; Reinerman et al. 2011; O'Connell and Bou-Matar 2007), consuming six to nine grams of cannabis per week (Bonn-Miller et al. 2014; Reinerman et al. 2011; O'Connell and Bou-Matar 2007), and prefer inhalation as the method of consumption (O'Connell and Bou-Matar 2007).

Studies also show that the majority of patients use medical cannabis to relieve pain. However, patients also report using cannabis to treat a variety of other conditions, including anxiety, sleep apnea, hypertension, incontinence, and depression (Aggarwal et al. 2013; Nunberg et al. 2011; Reinerman et al. 2011). Generally, patients report that medical cannabis is effective for helping them manage their condition(s) (Bonn-Miller et al. 2014; Ryan-Ibarra, Induni, and Ewing 2015; Aggarwal et al. 2013; Harris et al. 2000). For example, Aggarwal and colleagues (2013) found that, on a scale from 1 to 10, where 10 indicated absolute symptom control, patients reported that cannabis provided symptom control in the range of 7 to 10 across a variety of conditions. Patients also often reduce their use of other medications (i.e., prescription and over-the-counter drugs) when using medical cannabis (Nunberg et al. 2011; Aggarwal et al. 2009; Reiman 2009, 2007).

Though these studies are informative, one limitation is that most were conducted with samples of patients living in California. California patients may not represent those living in other areas of the country because the regulations that govern patients in California are different from those in other states. For example, residents of California may legally obtain medical cannabis to treat a number of ailments, including any chronic or persistent condition that considerably limits major life activities or that, if not alleviated, may compromise the patient's safety or health (California Senate Bill 420 2003). Because the list of conditions for which the legal medical use of cannabis is granted in other states is often less inclusive, patients from these states may differ from those in California.

Considering that medical cannabis has been legalized in many states, there is an opportunity to paint a more comprehensive picture of American medical cannabis patients by conducting similar studies in other geographic locations.

Scientists have begun to conduct such research through the examination of patients living in Washington State (Aggarwal et al. 2013, 2009) and Michigan (Ilgen et al. 2013). Our first goal was to continue this line of research by studying medical cannabis patients in Arizona. To aid comparisons with previous research, we assessed patient characteristics, behaviors, and perceptions that have been examined in prior studies. These included patterns of use (e.g., frequency of consumption, amount of consumption, preferred method of consumption), degree of relief experienced when using medical cannabis, and use of other medications.

In addition to the limited research on medical cannabis patients outside of California, to our knowledge there has been no systematic examination of patients' perceptions of the outcomes of medical cannabis legalization. One objective of legalizing cannabis for medical use is to safeguard its acquisition and production, which often involves strict regulation of its cultivation and sale. For instance, the rules and regulations of the Arizona Medical Marijuana Program require that those authorized to operate medical cannabis dispensaries and cultivation facilities enact strict security policies and procedures (Arizona Department of Health Services Medical Marijuana Rules 2012). In addition, many dispensaries and facilities employ third-party laboratories to test cannabis products for possible contaminants. However, it is unknown if such regulations translate to changes in patient safety or product quality.

Because individuals who use cannabis medicinally are those most affected by these regulations, surveying patients regarding their experiences purchasing and using medical cannabis may uncover the changes legalization has had on patient safety and product quality. In particular, patients with a history of using cannabis medicinally prior to legalization can provide their perspective on the changes that legalization has generated. The second goal of the present study was to determine the effectiveness of measures invoked to regulate and secure the cultivation and sale of medical cannabis by examining the perceptions of patients that used cannabis medicinally prior to legalization. Patients were asked to compare their perceptions of safety, product knowledge, and the effectiveness of cannabis for treating their condition(s) before and after legalization. Because of the regulations imposed with the legalization of medical cannabis, we hypothesized that patients would feel greater safety, have better knowledge, and that cannabis effectiveness would be greater after legalization.

METHOD

Participants and Procedures

Participants were 367 patients recruited from four medical cannabis dispensaries located throughout Arizona. The majority of the patients were male (63.8%), and

ranged from 18 to 83 years of age ($M = 45.78$ years; $SD = 13.76$ years). Most of the patients were White (86.4%), whereas the rest were Hispanic (6.3%), Black (2.5%), Native American (1.9%), Asian (0.8%), or Other (2.1%). These figures are similar to those reported by the Arizona Department of Health Services (2014) for this patient population.

To protect patient confidentiality, the authors did not directly contact patients, but approached dispensary owners to request assistance in recruiting participants. Dispensary owners informed their patients of the study, and interested patients were directed to a website that provided information about the research, including a description of the study, an explanation of patients' rights as participants, and information regarding the collection and storage of participant responses (i.e., responses were anonymous and would be stored on a password-protected server and/or computer only accessible to the researchers). If the patient agreed to participate, he or she checked a box indicating his or her agreement and the survey questions appeared.

Measures

Patient conditions. Participants were asked to select from an extensive list of conditions for which they use medical cannabis to control or treat. For each condition selected, participants completed subsequent questions and rated them on five-point Likert-type scales regarding the degree of relief experienced overall (1 = No relief at all; 5 = Almost complete relief), the degree of relief compared to other medications (1 = Much less relief; 5 = Much more relief), and the use of other medications since using medical cannabis (1 = I use other medications much less frequently; 5 = I use other medications much more frequently). Higher scores indicated greater relief or more frequent use of other medications.

Patterns and methods of cannabis use. Patients reported on the frequency ("On average, how frequently do you medicate with medical cannabis?": "Less than once per month" to "Several times per day") and amount ("On average, how much medical cannabis do you consume in a month?": "Less than one gram" to "More than one ounce") of consumption. Patients also completed a single-item measure regarding their preferred method of consumption (smoking, edibles, tinctures, vaporizing, raw consumption, or oils).

Perceptions of prior medical cannabis users. Participants were asked if they had used cannabis to treat their condition(s) before its legalization in Arizona. Those who replied "yes" were asked to complete four additional items. These items included the perceived safety of acquiring cannabis ("Compared to when you did not have a medical marijuana card, acquiring cannabis as a medical marijuana card holder feels": 1 = Much more dangerous; 5 = Much safer), knowledge of strain

characteristics ("Compared to when you did not have a medical marijuana card, your knowledge of what strain you are acquiring and its characteristics is": 1 = Much worse; 5 = Much better), confidence in a safe product ("Compared to when you did not have a medical marijuana card, your confidence that you are receiving a safe, uncontaminated product is": 1 = Much lower; 5 = Much higher), and product effectiveness for treating their condition(s) ("Compared to when you did not have a medical marijuana card, the effectiveness of the cannabis you receive to treat your condition is": 1 = Much worse; 5 = Much better).

RESULTS

The conditions for which patients reported using medical cannabis are displayed in Table 1. Consistent with previous research, the majority of patients reported suffering from chronic pain. Other commonly reported conditions included anxiety, depression, headaches, insomnia, muscle spasms, nausea, and stress.

Figure 1 shows the distributions of patients for frequency of cannabis use (Figure 1A), amount of cannabis consumed per month (Figure 1B), and preferred method of cannabis consumption (Figure 1C). The large majority of patients (83.7%) reported using medical cannabis several times per week or more, with most using medical cannabis daily (61%). Most patients consumed one-half of an ounce of cannabis or less per month (78.1%), and the most popular method of consumption was inhalation (i.e., smoking or vaporizing; 67.2%).

Perceived Effectiveness of Medical Cannabis

Patients' perceptions of the effectiveness of medical cannabis for treating their condition(s) are presented in Table 1. The values reflect the percent of patients who reported experiencing, overall, *a lot of relief* or *almost complete relief* from their symptoms and conditions when using medical cannabis (second column), *a little more relief* or *much more relief* from medical cannabis compared to other medications (third column), and using other medications *a little less frequently* or *much less frequently* when medicating with cannabis (fourth column).

For many of the conditions, patients reported that cannabis was effective for helping them manage their ailments. For example, at least 70% of patients reported experiencing *a lot of relief* or *almost complete relief* for 24 of the 42 conditions. Similarly, for 27 of the 42 conditions, at least 70% of patients reported experiencing *a little more relief* or *much more relief* from medical cannabis compared to other medications. Finally, at least 70% of patients reported using other medications *a little less frequently* or *much less frequently* for 24 of the 42 conditions.

TABLE 1
Percent of Patients Who Experience Relief and Less Frequently Use other Medications Due to Medical Cannabis Use, by Condition

Condition	Number of patients (%)	General relief ^a	Relief compared to other medications ^b	Less frequent use of other medications ^c
Alcohol Dependency	23 (6.3%)	91.30%	100%	100%
Anxiety	181 (49.3%)	82.90%	79.30%	85.90%
Arthritis	90 (24.5%)	63.30%	68.30%	81.20%
Asthma	13 (3.5%)	61.50%	50%	80.00%
ADHD	32 (8.7%)	81.20%	65%	84.60%
Bipolar Disorder	23 (6.3%)	60.90%	90.00%	56.30%
Bowel Distress	38 (10.4%)	78.90%	88.40%	95.40%
Cancer	17 (4.6%)	88.30%	54.60%	78.60%
Carpal Tunnel	15 (4.1%)	40.00%	80.00%	100%
Chronic Pain	318 (86.6%)	76.70%	73.50%	90.20%
Diabetes	26 (7.1%)	38.40%	37.50%	54.10%
Crohn's Disease	14 (3.8%)	85.70%	75%	81.80%
Depression	106 (28.9%)	82.10%	86.90%	65.10%
Fibromyalgia	26 (7.1%)	76.90%	76.20%	93.80%
Glaucoma	9 (2.5%)	55.50%	50.00%	60%
Headaches	106 (28.9%)	68.90%	73.70%	93.80%
Hepatitis C	11 (3.0%)	45.50%	85.80%	28.60%
HIV	1 (0.3%)	100%	100%	—
Huntington's Disease	1 (0.3%)	100%	—	—
Hypertension	26 (7.1%)	65.40%	60.00%	46.60%
Insomnia	145 (39.5%)	82.70%	77.40%	81.90%
Loss of Appetite	67 (18.3%)	79.10%	92.30%	88.90%
Multiple Sclerosis	5 (1.4%)	100%	75.00%	33.30%
Muscle Spasms	130 (35.4%)	76.20%	82.10%	91.40%
Muscular Dystrophy	1 (0.3%)	100%	100%	—
Nausea	105 (28.6%)	85.70%	87.30%	94.80%
Neuropathy	45 (12.3%)	51.10%	69.70%	60.70%
OCD	17 (4.6%)	64.70%	62.50%	33.40%
Opioid Dependency	8 (2.2%)	75%	60.00%	50.00%
Osteoarthritis	39 (10.6%)	61.50%	66.60%	84%
PTSD	28 (7.6%)	67.90%	92.90%	44.40%
Schizophrenia	2 (0.5%)	100%	100%	—
Seizures	15 (4.1%)	80.00%	61.60%	84.70%
Skin Conditions	5 (1.4%)	60.00%	50.00%	50.00%
Sleep Apnea	31 (8.5%)	58.10%	85.00%	66.60%
Stress	164 (44.7%)	87.20%	91.60%	79.10%
Tourette's Syndrome	4 (1.1%)	100%	100%	—
Tremors	6 (1.6%)	50.00%	100%	100%
Vomiting	31 (8.4%)	71.00%	87.50%	82.40%
Wasting	6 (1.6%)	50.00%	66.70%	100%
Weight Loss	24 (6.5%)	62.50%	80.00%	70.00%

^aThe percent of patients with this condition who reported that they experienced a lot or almost complete overall relief.
^bThe percent of patients with this condition who reported that they experienced a lot or almost complete overall relief.
^cThe percent of patients with this condition who reported that they use other medications a little or much less frequently.

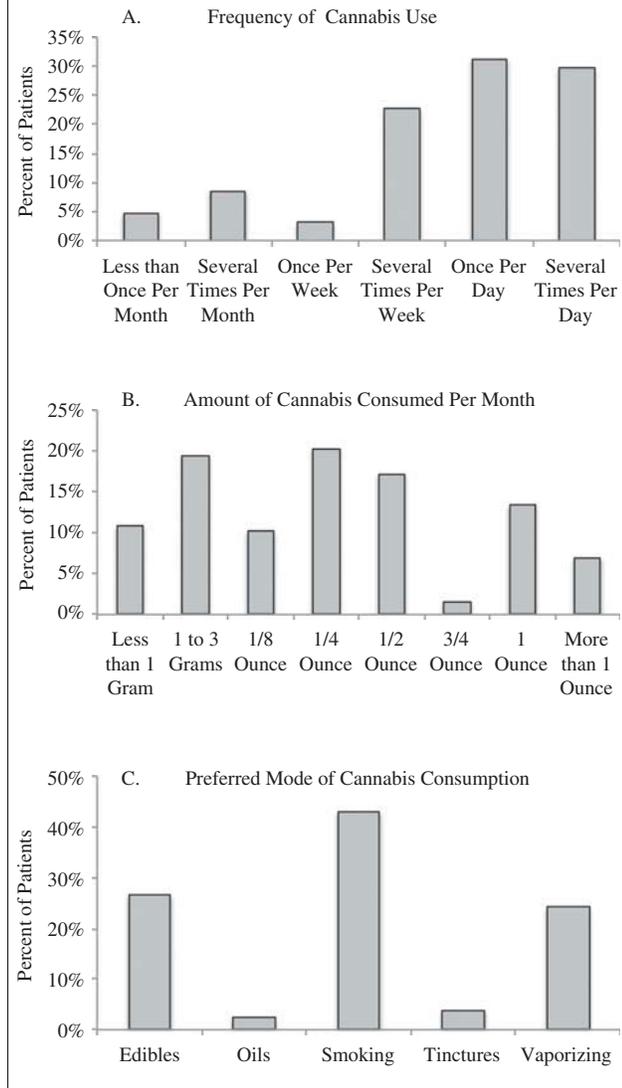
Perceived Effects of Medical Cannabis Legalization

Nearly two-thirds of participants (*n* = 239) reported using cannabis medicinally prior to legalization. These patients were asked to compare their current experiences

acquiring, their knowledge of, and their experiences using medical cannabis to their experiences and knowledge before legalization. Distributions of the patient's responses are shown in [Figure 2](#). Compared to their experiences

FIGURE 1

Distributions of patient responses, by percentage, for cannabis-related behaviors and perceptions: (A) the frequency of patient’s cannabis use; (B) the amount of cannabis consumed by patients per month; (C) patient’s preferred mode of cannabis consumption.



before legalization, 89.1% of patients reported that acquiring cannabis after legalization felt *somewhat safer* or *much safer*, 80.3% reported that their knowledge of the cannabis strains they acquired was *somewhat better* or *much better*, 85.4% reported that they had *somewhat more confidence* or *much more confidence* that they were purchasing a safe and uncontaminated product, and 79.5% reported that the medical cannabis was *somewhat more effective* or *much more effective* for treating their condition(s).

DISCUSSION

The goals of this study were to (1) examine the characteristics, perceptions, and behaviors of medical cannabis patients in Arizona; and (2) question participants with a history of cannabis use regarding their perceptions of safety acquiring cannabis, the quality of the cannabis they have obtained, their knowledge of the cannabis, and its perceived effectiveness, before and after legalization.

Patient Characteristics, Perceptions, and Behaviors

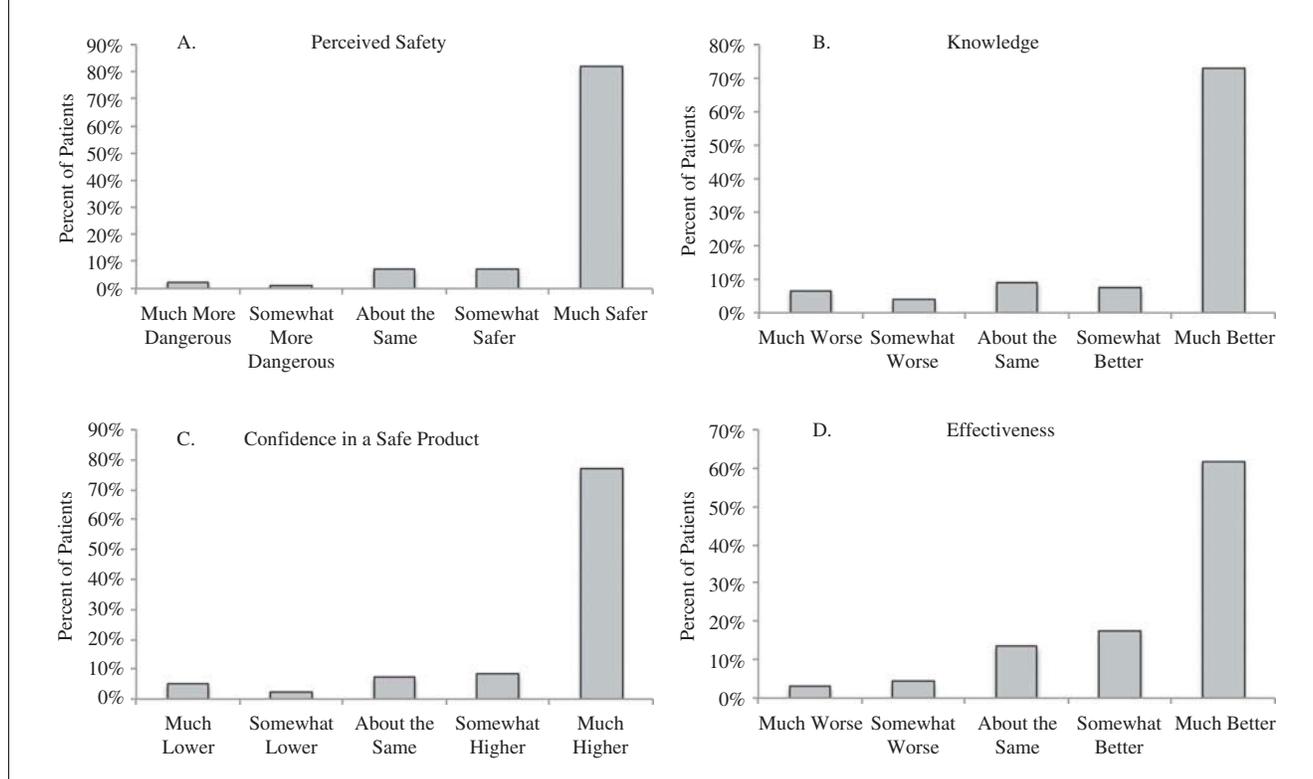
Consistent with research in other states (Bonn-Miller et al. 2014; Aggarwal et al. 2013; Ilgen et al. 2013; Nunberg et al. 2011; Reinerman et al. 2011; Aggarwal et al. 2009; Reiman 2009; O’Connell and Bou-Matar 2007; Harris et al. 2000), participants in the present study were mostly White men. Average patient age, approximately 46 years, differed from that in other states. For example, average ages reported in studies of patients from California range from 28 to 41 years (Bonn-Miller et al. 2014; Grella, Rodriguez, and Kim 2014; Reiman 2009, 2007; Harris et al. 2000). Average patient age is somewhat higher in Colorado (42 years of age; Colorado Department of Public Health and Environment 2014) and Washington State (41 to 47 years of age; Aggarwal et al. 2013, 2009). In Michigan (46 years of age; Murphy 2013) and Montana (47 years of age; Montana Department of Public Health and Human Services 2014), average patient age more closely approximates that of Arizona.

State-level variation in the average age of medical cannabis patients may in part be explained by the conditions that qualify a person to use medical cannabis in each state. For example, the qualifying conditions in Arizona, Colorado, Montana, Michigan, and Washington State are less inclusive than those in California, and are generally limited to more debilitating diseases. Individuals who suffer from more serious conditions may also be older, which may account for higher average patient ages in states other than California. The variability in these statistics underscores the risk of generalizing findings from patients living in California to those residing in other states and highlights the importance of studying patients throughout the United States. State-level differences in regulations also present an opportunity to explore how such regulations shape patient characteristics. A potential avenue for future work may be to study and compare patients in all states that have legalized the medical use of cannabis, ideally using a national sample to aid state-level comparisons.

Participants in the present study reported that, on average, they consumed cannabis on a daily basis and that inhalation was the preferred method of consumption, patterns of use that reflect those found in prior work (Bonn-Miller et al. 2014; Ilgen et al. 2013; Reinerman et al. 2011; O’Connell and Bou-Matar 2007). However, previous research shows that patients consume between

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FIGURE 2
Distributions of patient responses, by percentage, of their current experiences acquiring and knowledge of medical cannabis compared to their experiences before legalization: (A) the perceived safety of acquiring cannabis; (B) knowledge of medical cannabis characteristics; (C) perceived confidence in a safe product; and (D) perceived effectiveness of cannabis for treating their condition(s).



six and nine grams of cannabis per week or, equivalently, 0.85 to 1.25 ounces per month (Bonn-Miller et al. 2014; Reinerman et al. 2011; O’Connell and Bou-Matar 2007). This is in contrast to the findings of the present study, which show that 78% of patients consumed 0.5 ounces of cannabis per month or less.

State-level differences in average patient age, in particular, may affect variation in consumption. Patients in Arizona are, on average, older than those in California, and older patients may consume less cannabis than younger patients. Evidence from the present study supports this hypothesis, as there is a small, but significant, negative correlation between age and the amount of cannabis consumed per month ($r = -.11, p < .05$). Relatedly, Grella and colleagues (2014) found that younger patients visited dispensaries more frequently than older patients. Although there are likely other factors that contribute to consumption disparities, these findings also highlight the importance of studying medical cannabis patients across the US.

Patients reported using medical cannabis to treat a variety of conditions. The most commonly reported conditions included chronic pain, muscle spasms, nausea, anxiety, arthritis, depression, headaches, insomnia, and stress. Patients also reported that cannabis was effective for treating the symptoms of many of these conditions, findings that are consistent with previous research (Bonn-Miller et al. 2014; Ryan-Ibarra, Induni, and Ewing 2015; Aggarwal et al. 2013; Harris et al. 2000). This effectiveness included feelings of general relief and relief compared to other medications. The conditions for which the highest proportions of patients reported relief included alcohol dependency, anxiety, bowel distress, depression, insomnia, muscle spasms, and stress. Furthermore, patients reported using other medications less frequently when using cannabis. This is consistent with findings from other studies of patient perceptions (Reiman 2007, 2009; Nunberg et al. 2011; Reinerman et al. 2011), as well as a study of opiate overdose mortality, which showed that states with legalized medical cannabis had significantly lower opiate overdose mortality compared

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to those without legalized medical cannabis (Bachhuber et al. 2014).

Medical cannabis may benefit Arizona patients suffering from a variety of conditions. This conclusion has potential policy implications, as patients report deriving benefit not only for conditions that fall under the list of conditions that qualify a person to use medical cannabis (e.g., cancer, chronic pain, muscle spasms), but also for conditions that are not listed (e.g., anxiety, depression, insomnia). Officials in Arizona previously considered research on post-traumatic stress disorder (PTSD; Greer, Grob, and Halberstadt 2014) in their decision to include PTSD among Arizona's qualifying conditions. Thus, officials may consider the findings from the present study, in conjunction with other research, to determine the suitability of expanding the list of qualifying conditions in Arizona.

Legalization and Patient Experiences

The present study was, to our knowledge, the first to examine the effect of legalization on patient's experiences with medical cannabis. Regarding safety, the majority of patients reported feeling safer acquiring medical cannabis after legalization, and their confidence that they were acquiring a safe, uncontaminated product was higher. Patients also reported that their knowledge of the strains they acquired was better and that the cannabis they acquired after legalization was more effective for treating their condition(s) than the cannabis they acquired before legalization.

These findings show that the Arizona medical cannabis program has had some success, as regulations have provided a safe environment for patients to acquire a safe and high-quality product. However, the potential negative effects of medical cannabis legalization were not assessed in the present study. For example, participants in other studies have reported difficulties affording legal medical cannabis (Aggarwal et al. 2009), a factor which may preclude some individuals from taking advantage of the program, leaving them seeking other, potentially illegal means of cannabis acquisition. Other factors, such as limits on the amount of cannabis that can be purchased or legal

issues related to medical cannabis use, may also have negative consequences for some segments of the patient population.

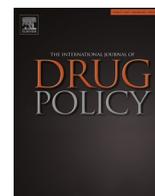
The results of this study should be considered in light of some limitations. First, participant recruitment was conducted through medical cannabis dispensaries. Although this is a common method of recruitment (e.g., Bonn-Miller et al. 2014; Grella, Rodriguez, and Kim 2014; Aggarwal et al. 2013; Reiman 2009, 2007; Harris et al. 2000), such samples may have a positive bias for medical cannabis, as individuals who medicate with cannabis but for whom it was not effective are unlikely to be available to participate. However, at least one study using a large, representative sample of current and former medical cannabis users reported similar findings (Ryan-Ibarra, Induni, and Ewing 2015), lending validity to the results of the present study and those of previous research. Second, relatively few patients reported using medical cannabis for some of the conditions. Although this is not surprising, given the low incidence of some conditions, conclusions should be tempered for these conditions with respect to the effectiveness of medical cannabis for providing relief and/or for use as a substitute for other medications. Finally, patients' experiences acquiring and their knowledge of medical cannabis before and after legalization were assessed retrospectively, using a single measurement time-point.

Despite these limitations, this study has significance for understanding the characteristics, behaviors, and perceptions of Arizona medical cannabis patients. Additionally, it highlights the importance of studying patients throughout the US and understanding the potential effects of state-level regulatory differences on patient populations. The findings regarding the effectiveness of cannabis for treating various conditions have potential policy implications for the state of Arizona, as patients reported that cannabis was effective for treating conditions that currently do not qualify individuals for medical cannabis use. Furthermore, the results showed that the majority of patients report positive experiences as a result of legalization, although more work is needed to fully understand the consequences of Arizona's medical cannabis program.

REFERENCES

- Aggarwal, S. K., G. T. Carter, M. D. Sullivan, C. Zubrunnen, R. Morrill, and J. D. Mayer. 2009. Characteristics of patients with chronic pain accessing treatment with medical cannabis in Washington State. *Journal of Opioid Management* 5 (5):257–86.
- Aggarwal, S. K., G. T. Carter, M. D. Sullivan, C. Zubrunnen, R. Morrill, and J. D. Mayer. 2013. Prospectively surveying health-related quality of life and symptom relief in a lot-based sample of medical cannabis-using patients in urban Washington State reveals managed chronic illness and debility. *American Journal of Hospice and Palliative Medicine* 30 (6):523–31. doi:10.1177/1049909112454215.
- Allegretti, J. R., A. Courtwright, M. Lucci, J. R. Korzenik, and J. Levine. 2013. Marijuana use patterns among patients with inflammatory bowel disease. *Inflammatory Bowel Diseases* 19 (13):2809–14. doi:10.1097/01.MIB.0000435851.94391.37.
- Anderson Robbins Research & Shaw & Company Research. 2013. Fox News poll: 85 percent of voters favor medical marijuana [survey report]. *Fox News*. <http://www.foxnews.com/politics/interactive/2013/05/01/fox-news-poll-85-percent-voters-favor-medical-marijuana/>
- Arizona Department of Health Services. 2014. Arizona Medical Marijuana Act End of Year Report. <http://www.azdhs.gov/>

- medicalmarijuana/documents/reports/2014/arizona-medical-marijuana-end-of-year-report-2014.pdf
- Arizona Department of Health Services Medical Marijuana Rules. 2012. http://www.azsos.gov/public_services/Title_09/9-17.htm
- Associated Press-CNBC. 2010. AP-CNBC marijuana poll: Complete results & analysis. April 7-12, 2010 [Survey Report]. *CNBC News*. <http://www.cnbc.com/id/36601126#>
- Aviello, G., B. Romano, F. Borrelli, R. Capasso, L. Gallo, F. Piscitelli, V. Di Marzo, and A. A. Izzo. 2012. Chemopreventive effect of the non-psychoactive phytocannabinoid cannabidiol on experimental colon cancer. *Journal of Molecular Medicine* 90 (8):925–34. doi:10.1007/s00109-011-0856-x.
- Bachhuber, M. D., B. Saloner, C. O. Cunningham, and C. L. Barry. 2014. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *Journal of the American Medical Association* 311 (10):1668–73.
- Bar-Sela, G., M. Vorobeichik, S. Drawsheh, A. Omer, V. Goldberg, and E. Muller. 2013. The medical necessity for medicinal cannabis: Prospective, observational study evaluating the treatment in cancer patients on supportive or palliative care. *Evidence-Based Complementary and Alternative Medicine* 2013:1–8. doi:10.1155/2013/510392.
- Bonn-Miller, M. O., M. T. Boden, M. M. Bucossi, and K. A. Babson. 2014. Self-reported cannabis use characteristics, patterns and helpfulness among medical cannabis users. *The American Journal of Drug and Alcohol Abuse* 40 (1):23–30. doi:10.3109/00952990.2013.821477.
- California Senate Bill 420. 2003. http://www.leginfo.ca.gov/pub/03-04/bill/sen/sb_0401-0450/sb_420_bill_20031012_chaptered.html
- Colorado Department of Public Health and Environment. 2014. Medical Marijuana Registry Program Update. https://www.colorado.gov/pacific/sites/default/files/CHED_MMJ_06_2014_MMR_report.pdf
- Greer, G. R., C. S. Grob, and A. L. Halberstadt. 2014. PTSD symptom reports of patients evaluated for the New Mexico medical cannabis program. *Journal of Psychoactive Drugs* 46 (1):73–77. doi:10.1080/02791072.2013.873843.
- Grella, C. E., L. Rodriguez, and T. Kim. 2014. Patterns of medical marijuana use among individuals sampled from medical marijuana dispensaries in Los Angeles. *Journal of Psychoactive Drugs* 46 (4):263–72. doi:10.1080/02791072.2014.944960.
- Harris, D., R. T. Jones, R. Shank, R. Nath, E. Fernandez, K. Goldstein, and J. Mendelson. 2000. Self-reported marijuana effects and characteristics of 100 San Francisco medical marijuana club members. *Journal of Addictive Diseases* 19 (3):89–103. doi:10.1300/J069v19n03_07.
- Ilgel, M. A., K. Bohnert, F. Kleinberg, M. Jannausch, A. S. B. Bohnert, M. Walton, and F. C. Blow. 2013. Characteristics of adults seeking medical marijuana certification. *Drug and Alcohol Dependence* 132 (3):654–59. doi:10.1016/j.drugalcdep.2013.04.019.
- Jiang, W., Y. Zhang, L. Xiao, J. V. Cleemput, S. Ji, G. Bai, and X. Zhang. 2005. Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. *Journal of Clinical Investigation* 115 (11):3104–16. doi:10.1172/JCI25509.
- Lorenz, R. 2004. On the application of cannabis in paediatrics and epileptology. *Neuro Endocrinology Letters* 25 (1-2): 40–44.
- Lynch, M. E., and F. Campbell. 2011. Cannabinoids for treatment of chronic non-cancer pain: A systematic review of randomized trials. *British Journal of Clinical Pharmacology* 72 (5):735–44. doi:10.1111/j.1365-2125.2011.03970.x.
- Montana Department of Public Health and Human Services. 2014. Montana Marijuana Program December 2014 Registry Information. <http://dphhs.mt.gov/Portals/85/qad/documents/LicensureBureau/Marijuana%20Program/MMP%20Registry%20Information%20through%20December%2030%202014.pdf>
- Murphy, R. 2013. 2013 update: Michigan medical marijuana. <http://marijuanapatient.org/michigan-comparison/>
- Nunberg, H., B. Kilmer, R. L. Pacula, and J. R. Burgdorf. 2011. An analysis of applicants presenting to a medical marijuana specialty practice in California. *Journal of Drug Policy Analysis* 4 (1):1–16. doi:10.2202/1941-2851.1017.
- O’Connell, T. J., and C. B. Bou-Matar. 2007. Long term marijuana users seeking medical cannabis in California (2001-2007): Demographics, social characteristics, patterns of cannabis and other drug use of 4117 applicants. *Harm Reduction Journal* 4 (16). doi:10.1186/1477-7517-4-16.
- Reiman, A. 2007. Medical cannabis patients: Patient profiles and health care utilization patterns. *Complementary Health Practice Review* 12 (1):31–50.
- Reiman, A. 2009. Cannabis as a substitute for alcohol and other drugs. *Harm Reduction Journal* 6 (1):35. doi:10.1186/1477-7517-6-35.
- Reinarman, C., H. Nunberg, F. Lanthier, and T. Heddleston. 2011. Who are medical marijuana patients? Population characteristics from nine California assessment clinics. *Journal of Psychoactive Drugs* 43 (2):128–35. doi:10.1080/02791072.2011.587700.
- Ryan-Ibarra, S., M. Induni, and D. Ewing 2015. Prevalence of medical marijuana use in California, 2012. *Drug and Alcohol Review* 34 (2):141–146.



Research paper

Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients

Philippe Lucas^{a,b,c,*}, Zach Walsh^{d,e}^a Tilray, 1100 Maughan Rd., Nanaimo, BC V9X1J2, Canada^b Social Dimensions of Health, University of Victoria, 3800 Finnerty Rd., Victoria, BC V8P 5C2, Canada^c Centre for Addictions Research of British Columbia, 2300 McKenzie Ave, Victoria, BC V8N 5M8, Canada^d Department of Psychology, University of British Columbia, Okanagan, 3333 University Way, Kelowna, BC V1V 1V7, Canada^e Centre for the Advancement of Psychological Science and Law, University of British Columbia, Okanagan, 3333 University Way, Kelowna, BC V1V 1V7, Canada

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ABSTRACT

Background: In 2014 Health Canada replaced the Marihuana for Medical Access Regulations (MMAR) with the Marihuana for Medical Purposes Regulations (MMPR). One of the primary changes in the new program has been to move from a single Licensed Producer (LP) of cannabis to multiple Licensed Producers. This is the first comprehensive survey of patients enrolled in the MMPR.

Methods: Patients registered to purchase cannabis from Tilray, a federally authorized Licenced Producer (LP) within the MMPR, were invited to complete an online survey consisting of 107 questions on demographics, patterns of use, and cannabis substitution effect. The survey was completed by 271 respondents.

Results: Cannabis is perceived to be an effective treatment for diverse conditions, with pain and mental health the most prominent. Findings include high self-reported use of cannabis as a substitute for prescription drugs (63%), particularly pharmaceutical opioids (30%), benzodiazepines (16%), and antidepressants (12%). Patients also reported substituting cannabis for alcohol (25%), cigarettes/tobacco (12%), and illicit drugs (3%). A significant percentage of patients (42%) reported accessing cannabis from illegal/unregulated sources in addition to access via LPs, and over half (55%) were charged to receive a medical recommendation to use cannabis, with nearly 25% paying \$300 or more.

Conclusion: The finding that patients report its use as a substitute for prescription drugs supports prior research on medical cannabis users; however, this study is the first to specify the classes of prescription drugs for which cannabis it is used as a substitute, and to match this substitution to specific diagnostic categories. The findings that some authorized patients purchase cannabis from unregulated sources and that a significant percentage of patients were charged for medical cannabis recommendations highlight ongoing policy challenges for this federal program.

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Background

The past two decades have witnessed a resurgence of interest in the therapeutic potential of cannabis, with several nations and jurisdictions developing regulations to allow for access to cannabis for medical purposes (Fischer, Murphy, Kurdyak, Goldner, & Rehm, 2015). One potential salutary consequence of these developments

is the substitution of cannabis for other substances (Allsop et al., 2014; Lucas et al., 2013, 2016). Indeed, examinations of jurisdictions with legal access to medical cannabis have reported reductions in negative health outcomes associated with the use of other substances, such as opioid overdose (Bachhuber, Saloner, Cunningham, & Barry, 2014), and cannabis substitution has been forwarded as a mechanism to help explain these public health benefits. Consistent with this proposal, several large surveys confirm that medical cannabis users report substituting cannabis for other medications (Lucas, 2012a; Lucas et al., 2013, 2016; Reiman, 2009). Although extant surveys have provided broad evidence of cannabis substitution, the extent to which cannabis is

* Corresponding author at: Social Dimensions of Health, University of Victoria, 3800 Finnerty Rd., Victoria, BC, V8P 5C2, Canada.

E-mail addresses: plucas@uvic.ca, philippe@tilray.ca (P. Lucas).

used to substitute for distinct classes of substances by distinct patient groups has not been systematically examined from a patient-centred perspective. The present study addresses this knowledge gap by examining the extent to which physician-authorized medical cannabis users report using cannabis as a substitute for specific classes of substances, and by disaggregating this examination according to condition-based patient group. We also add to the nascent literature on medical cannabis use by describing patient characteristics, patterns of use and barriers to access.

In 2001 Canada became one of the first nations to develop a program to allow access to cannabis for medical purposes. The program has undergone numerous convolutions, culminating in the 2014 establishment by Health Canada of the Marihuana for Medical Purposes Regulations (MMPR) (Walsh et al., 2013), and ultimately in the Access to Cannabis for Medical Purposes Regulations in August 2016. One of the primary changes of the MMAR was the authorization of multiple Licensed Producers of cannabis: as of August 2016 >30 federally authorized Licensed Producers provide hundreds of strains of cannabis, as well as cannabis extracts to approximately 67,075 patients (Office of Medical Cannabis, 2016). The ACMPR adds regulations by which patients can produce their own cannabis, an option that was removed in the transition from MMAR and MMPR, and subsequently re-established through a court decision (Allard et al. v. Canada).

In contravention of the MMPR/ACMPR, a large number of patients access cannabis through community-based outlets known as dispensaries or compassion clubs, as well as from friends and other sources. In addition, although many Provincial medical colleges expressly forbid physicians from charging patients for providing patients with medical cannabis prescriptions, 3rd party patient aggregator services have emerged that provide cannabis prescriptions, occasionally in exchange for a substantial fee. To date, the prevalence of this practice among clients of LPs has not been explicitly examined. In addition to providing a more granular examination of cannabis substitution, this study also adds to the growing literature chronicling patterns of medical cannabis use and user characteristics using a novel sampling methodology: whereas prior studies generally queried self-identified medical cannabis users who may not have obtained physician authorization (Lucas, 2012b; Lucas et al., 2013; Walsh et al., 2013), to our knowledge this is the first study since the establishment of the MMPR to include only those medical cannabis users with confirmed physician authorization to access cannabis for therapeutic purposes.

Design and methods

A password protected 107 question online cross-sectional survey was made available in French and English for a 2 week period in July 2015 to patients of Tilray—a licensed producer of cannabis. 1310 participants were notified of the opportunity to participate in this study via direct email to patients that had opted in to receive online communication from Tilray upon registration. Participants were compensated \$10 credit for Tilray cannabis. The study was approved by Institutional Review Board Services, and gathered data on demographics, patient experiences, patterns of use, and cannabis substitution effect. Respondents were not forced to answer a given question in order to proceed to the next and as such the number of recorded responses varies across items. All reported percentages are based on number of responses rather than on the entire sample; we accompany all reported percentages with number of responses.

Findings

The survey was started by 301 participants, and completed by over 90% of respondents ($n=271$). The 30 non-completers only filled out the demographic section of the study, and based on this information did not differ on age, gender, education, income or work status compared to those that completed the survey. The primary demographics of respondents corresponds with the greater Tilray patient population but was more male and Caucasian, single, disabled and of lower income than the general Canadian population, with over-representation in Western Canada and Ontario, and under-representation in Quebec (see Table 1 for demographic characteristics).

While an increasingly common medical treatment, cannabis is often used for symptom relief rather than as a curative agent, therefore it's important to distinguish between the primary conditions for which cannabis is officially prescribed by a physician, and the specific symptoms for which patients report relief. For example, while a patient might report having a prescription for MS, the list of symptoms impacted might include chronic pain, spasticity, and insomnia. In this survey, respondents could select a single primary condition from a drop-down list, but could then select multiple symptoms affected by the medical use of cannabis. In regards to conditions, pain-related conditions were the most common, reported by 53% of participants ($n=144$; chronic pain 36%; ($n=98$), arthritis 12% ($n=32$), headache 5% ($n=14$)). The second most prominent class was mental health (eating disorder, PTSD & psychiatric disorder), reported by 15% ($n=41$). Other prominent conditions included gastrointestinal I disorders (11%, $n=29$), insomnia (7%, $n=18$) and multiple sclerosis (4%, $n=11$).

In regards to symptoms; the most highly endorsed were chronic pain (73%, $n=197$), stress (60%, $n=162$), insomnia (57%, $n=155$), depression (46%, $n=126$) and headache (32%, $n=87$). Gastrointestinal (GI) issues also featured prominently, with 29% ($n=79$) citing appetite loss and another 29% ($n=79$) nausea. Cannabis was perceived to be very effective at symptom relief, with 95% ($n=257$) reporting that it “often” or “always” helped alleviate their symptoms.

Patterns of use

The mean age of initiation was 18.50 (SD = 7.42) for recreational use and 34.13 (SD = 13.74) for medical use, as determined by responses to the question “How old were you when you first used cannabis” followed by “How old were you when you first used cannabis for medical purposes?”. It is notable that participants readily distinguished between their recreational and medical use of cannabis, with recreational cannabis use preceding medical use for 81% ($n=220$) of respondents, with 16% ($n=44$) reporting no history of recreational cannabis use, and 3% ($n=7$) reporting precedence of medical use prior to recreational use.

In regard to frequency, 88% ($n=238$) reported using cannabis at least daily, and the modal amount used per day was 1–2 g, with 29% ($n=79$) using a larger amount.

In regard to methods of use, 90% ($n=243$) had tried joints, 86% ($n=234$) vaporizers, 76% ($n=207$) oral/edibles (such as baked goods, butter, tincture, etc.) and 16% ($n=44$) had used cannabis-infused topical ointments. Regarding primary methods of use, vaporizers proved most popular (38%, $n=102$), followed by joints (25%, $n=67$), oral/edibles (14%, $n=37$), waterpipe/bongs (12%, $n=33$), pipes (11%, $n=30$), and topicals (1%, $n=2$). Regarding preferred method, vaporization was rated most highly by a plurality (44%, $n=119$), with oral/edibles second (23%, $n=63$). Respondents overwhelmingly reported that not all strains/types of cannabis were “equally effective” at relieving symptoms (77%, $n=210$): 82%

Table 1
Demographics.

	Tilray, survey respondents (n = 271) (%)	Tilray, all patients (n = 3077) ^a (%)	Canadian average, stats Canada, 2011 census ^b (%)
Gender			
Male	73	70	49
Female	27	30	51
Age	(Range: 20–77)		
Mean	40	44	41
Background			
Caucasian	94	N/A	77
Black	4	N/A	3
Aboriginal/Metis	3	N/A	4
South Asian	2	N/A	5
Asian	2	N/A	5
Marital status			
Married	43	N/A	46
Domestic partnership/civic union	9	N/A	11
Divorced/separated	10	N/A	8
Single	38	N/A	28
Education			(Age 25–64)
Less than high school	7	N/A	13
High school or equivalent	20	N/A	23
Some college/university	21	N/A	N/A
Technical and/or non-university degree	28	N/A	21
University degree	15	N/A	17
Graduate degree	8	N/A	10
Employment			15 years and over
Employed, full time	45	N/A	51
Employed, part time	12	N/A	12
Disabled	30	N/A	14
Not employed	8	N/A	7.8
Retired	5	N/A	N/A
Income			
Less than \$10,000	9	N/A	5
\$10,000–39,999	32	N/A	27
\$40,000–99,999	40	N/A	42
>\$100,000	19	N/A	26
Province of residence			
Prairies	24	19	18
British Columbia	17	22	13
Atlantic	8	7	7
Territories	1	1	1
Ontario	49	49	38
Quebec	2	2	24

^a As of July 31, 2015.^b Statistics Canada. Canadian census, 2011. <https://www12.statcan.gc.ca/census-recensement/2011/dp-pd/prof/index.cfm?Lang=E>.

(n = 222) reported a preferred cannabis type; 25% (n = 68) indicas, 21% hybrids (n = 56), 18% favoring strains high in cannabidiol (CBD) (n = 50), and 18% sativas (n = 48). While many Licensed Producers continue to identify cannabis by these phenotypes (*Cannabis sativa* and *Cannabis indica*) in keeping with classifications found in the black market, there is a growing academic debate about whether these classifications represent real and distinct genetic classifications, with evidence suggesting that the label of indica or sativa is not consistent with the actual genetics of many of these strains (Sawler et al., 2015). However, evidence that cannabinoids and terpenes are found at different ratios within each distinct cannabis phenotype supports the subjective differences between strains commonly reported by patients.

Cannabis substitution effect

Overall, 71% (n = 186) of participants report substituting cannabis for either prescription drugs, alcohol, tobacco/nicotine or illicit substances, with 63% reporting substitution for

prescription medication (n = 166), 25% for alcohol (n = 66), 12% for tobacco/nicotine (n = 31), and 3% for illicit substances (n = 9). To facilitate interpretation of substitution for prescription medications, pharmaceuticals were classed into the following 4 categories: *opioids*, *benzodiazepines*, *antidepressants* and a category of *other medication* that included diverse substances that were less frequently endorsed (e.g., NSAIDs, Methylphenidate). Respondents were allowed to report up to three medications for which they substituted cannabis; of those who explicitly listed prescription substitution 59% (n = 92) reported substituting for a single class of medications, 33% (n = 52) reported substituting for two classes, and 8% (n = 13) reported substituting cannabis for three classes. The most common form of substitution was for opioids (32%, n = 80), followed by benzodiazepines (16%, n = 40), and antidepressants (12%, n = 31) (Table 2). The reasons most frequently ranked as being most important for substituting cannabis for prescribed medications were “less adverse side effect” (39%, n = 68); “cannabis is safer” (27% n = 48), and “better symptom management” (16%, n = 28).

Table 2
Substitution for prescription medications.

Class	n	%
Opioids (Oxy/Oxyneo/Percocet/hydromorphone/morphine/codeine derivatives, etc.)	80	32
Benzodiazepines	40	16
Antidepressants	31	12
Other medication	100	40

Supplementary analyses examined variation across diagnostic groups, and indicated that respondents who used cannabis for pain-related conditions were more likely to substitute cannabis for opioids (42% (n = 57) vs. 20% (n = 23), $\chi^2 = 13.78(1)$, $p < 0.01$), whereas respondents who used cannabis to address mental health were more likely to substitute cannabis for benzodiazepines (31% (n = 12) vs. 13% (n = 28), $\chi^2 = 7.75(1)$, $p < 0.01$) and for antidepressants (26% (n = 10) vs. 10% (n = 21), $\chi^2 = 7.69(1)$, $p = 0.01$) (Fig. 1). Our data suggested no relationship between age, amount of cannabis used, mode of administration, access or affordability on substitution effect.

Access

Although all respondents accessed cannabis from Tilray, 21% (n = 56) also reported purchasing cannabis from another Licensed Producer, 25% (n = 67) purchased from dispensaries, 18% (n = 47) from a friend, and 8% (n = 20) buy from an illicit dealer. In total, 42% (n = 111) of respondents reported accessing from one or more unregulated sources. Regarding cost, 44% (n = 118) spend less than \$250 monthly and 78% (n = 212) spend less than \$500 per month on cannabis, whereas 4% spend \$1000 or more (n = 11). Capacity to “often” or “always” afford to buy enough cannabis to relieve symptoms was reported by 40% (n = 109), leaving 60% (n = 162) who report “sometimes” or “never” affording sufficient cannabis. Similarly, 53% (n = 146) reported choosing between medical cannabis and other necessities (food, rent, other medicines . . .) in the past year due to finances. Only 3% (n = 7) cited having 3rd party insurance coverage, and another 3% (n = 8) reported getting the cost of cannabis covered through Veterans Affairs Canada.

Finding a supportive physician was a reported challenge, with 31% (n = 78) having changed doctors in relation to medical cannabis use, and 55% reporting feeling discriminated against by their doctor because of medical cannabis use (n = 139). Paying a physician or clinic a fee for recommendations to use medical cannabis was reported by 55% (n = 140), with a modal price of between \$300–99 (n = 50) and

94% (n = 131) paying \$100 or more. It is therefore unsurprising that 29% (n = 75) reported that obtaining an authorization to use medical cannabis was “difficult” or “very difficult”.

Interpretation

The finding that patients using cannabis to treat pain-related conditions have a higher rate of substitution for opioids, and that patients self-reporting mental health issues have a higher rate of substitution for benzodiazepines and antidepressants has significant public health implications. In light of the growing rate of morbidity and mortality associated with these prescription medications (Bachhuber et al., 2014; Fischer, Rehm, Goldman, & Popova, 2008), cannabis could play a significant role in reducing the health burden of problematic prescription drug use. Indeed, a recent study of US states that have legalized medical cannabis, found that the number of prescriptions significantly dropped for drugs that treat pain, depression, anxiety, nausea, psychoses, seizures and sleep disorders, with the annual number of doses prescribed for chronic pain falling by more than 11% per physician (Bradford & Bradford, 2016). Additionally, according to Veterans Affairs Canada, a recent significant increase in the use of medical cannabis by patients is paralleled by a nearly 30% decrease in the use of benzodiazepines and a 16% decrease in the use of opioids (Hager, 2016). Moreover, the finding that cannabis might be used to substitute for multiple medications is particularly promising in light of concerns patients may have regarding adherence to complex pharmaceutical regimens, and attendant side effects (Brown & Bussell, 2011; Ingersoll & Cohen, 2008; Sylvestre, Clements, & Malibu, 2006). Indeed, tolerability of side effects was identified as a prominent reason for cannabis substitution.

The finding that medical cannabis is used primarily to treat chronic pain is consistent with past research (Ware et al., 2010; Ware, Wang, Shapiro, & Collet, 2015). However, the extensive self-

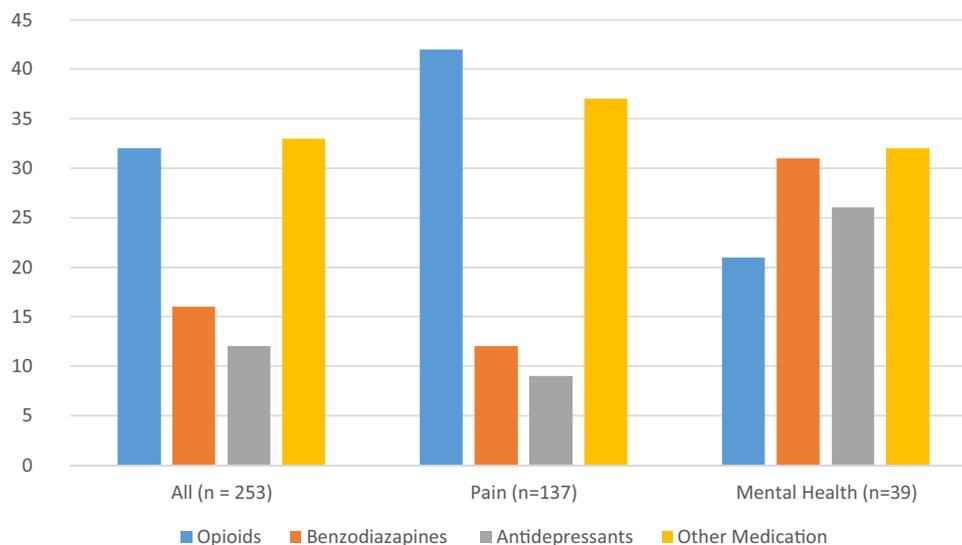


Fig. 1. Substitution by condition.

reported use to treat mental health conditions and associated symptoms represents a novel and interesting trend, and suggests that the conceptualization of cannabis as deleterious to mental health may not generalize across conditions or populations. Studies currently underway to investigate cannabis for the treatment of PTSD, anxiety, and other psychiatric conditions may soon provide more information on these potentially promising treatment options.

Our finding that most patients use 2 grams or less is consistent with past research (Carter, Weydt, Kyashna-Tocha, & Abrams, 2004; Clark, 2013; Hazekamp, Ware, Muller-Vahl, Abrams, & Grotenhermen, 2013). To our knowledge, this is the first patient survey to report vaporization as the primary method of ingestion, and non-smoked forms of ingestion as primary and preferred methods of ingestion. This marks a health conscious shift in medical cannabis use under the MMPR that may be attributed to a few factors: since patients in the MMPR require a physicians support to access medical cannabis, they may be more likely to be focused on safer methods of ingestion than non-MMPR patient populations; improvements in vaporizer technology and associated reductions in cost, patient outreach and education initiatives focused on safe and responsible use by cannabis vendors, and ongoing restrictions on smoking in the public realm.

Cannabis is rather unique as a therapeutic treatment in that many patients report some permeability between recreational and medical use (Walsh et al., 2013). However, unlike opioids where medical use via prescription often precedes recreational use and dependence (Fischer et al., 2008), the pathways between the medical and recreational use of cannabis are reversed, with previous recreational use often a precursor to prescription medical use, while the reverse is rarely the case. Although most respondents in this study had experience with recreational cannabis use prior to initiation of medical use (81%, $n=220$), transition from medical use to recreational use was only reported by 7 participants (<3%), which is suggestive of a low risk of abuse associated with medical cannabis. Additionally, with so many patients reporting use for the relief of mental health conditions like stress, insomnia and depression, much of this medical use is ultimately focused on improving psychological well being and quality of life. This perhaps blurs the lines between traditional biomedical approaches to disease and more holistic approaches (such as yoga or naturopathic medicine) used as adjunct treatments to address the symptoms, side-effects and psychological impacts of long-term illness/disability and/or the modern pressures of every day life. This is supported by previous research that has found that patients who use medical cannabis often cite depression and anxiety as a primary symptoms for which they seek relief, regardless of their actual medical condition (Bonn-Miller, Boden, Bucossi, & Babson, 2014; Ogborne, Smart, Weber, & Birchmore-Timney, 2000; Walsh et al., 2016), as well a growing amount of preclinical research supporting the use of CBD as a potential treatment for both anxiety (Blessing, Steenkamp, Manzanares, & Marmar, 2015) and depression (Linge et al., 2015).

Despite the legal protection and quality control offered through the MMPR, 42% of participants report accessing cannabis from unregulated sources which may be due to restrictions imposed on LPs by the MMPR during that period. At the time of this survey, LPs were only allowed to provide raw cannabis flowers, whereas other sources may have provided a diverse array of extracts and edibles. Since that time regulations have been altered to allow LPs to produce extracts, and to once again produce their own cannabis supply. Future research may determine whether this regulatory revision alters patient behaviour in regards to access through unregulated sources.

In light of consistent evidence that many lower income patients face affordability issues in regards to the cost of medical cannabis (Belle-Isle et al., 2014), the finding that so many patients had to pay high medical fees to gain access medical cannabis is concerning and suggests there may subsequently be an under-representation of low income patients in the MMPR/ACMPR.

Conclusions

The high rate of substitution for prescription drugs among patients with pain-related and mental health conditions suggests that medical cannabis may be an effective adjunct or substitute treatment to prescription drugs used to treat these conditions. Further research into the comparative efficacy of cannabis relative to front-line treatments for these conditions is warranted, and longitudinal research would help elucidate the context of cannabis substitution effect, and the potential impact of cannabis substitution on the quality of life of patients (in-progress, Lucas).

While the MMPR had only been in place for approximately 15 months when this survey took place, the findings that some authorized patients continue to purchase cannabis from unregulated sources and that a significant percentage of patients have had to pay high fees for medical cannabis recommendations highlight ongoing policy challenges for the federal medical cannabis program. As Canada's federal medical cannabis policy continues to evolve (both organically and in response to legal challenges) and as provinces and municipalities seek regulatory solutions to issues like dispensaries, personal production, and private medical cannabis clinics, it will be important to keep tracking the impact of these policy developments on patient access to and experiences with medical cannabis.

Limitations

The relatively low response rate to the survey (21%) leaves open the possibility this could potentially be an unrepresentative sample. It is not possible to confirm the impact of cannabis substitution on quantity of use of prescription drugs, alcohol or illicit drug use. Additionally, all data regarding the cannabis substitution effect in this study were self-reported by patients and did not benefit from biological drug detection to confirm use or non-use of a substance. In light of this potential bias, our characterisation of the therapeutic use of cannabis and/or cannabis substitution effect should be interpreted with caution pending replication by research that employs a more systematic recruitment approach, longitudinal monitoring, and biological drug testing.

However, these limitations are counterbalanced by several methodological strengths, including the large size of the sample, assurance that all participants were using medical cannabis with the support of a physician, and adherence to established standards for reporting Internet-based surveys (Eysenbach, 2004).

Declaration of interest

This study was funded by Tilray, a federally authorised medical cannabis production and research company. Philippe Lucas is currently employed as Vice-President, Patient Research and Advocacy for Tilray; however, his compensation is not tied in any way to the outcomes of this study.

Zach Walsh is currently the Primary Investigator in a Tilray-sponsored randomized clinical trial of medical cannabis and PTSD, but he receives no financial compensation for that study nor for assisting with the analysis and writing of this paper.

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References

- Allsop, D. J., Dunlop, A. J., Saddler, C., Rivas, G. R., McGregor, I. S., & Copeland, J. (2014). Changes in cigarette and alcohol use during cannabis abstinence. *Drug and Alcohol Dependence*, 138(1), 54–60. <http://dx.doi.org/10.1016/j.drugalcdep.2014.01.022>.
- Bachhuber, M. A., Saloner, B., Cunningham, C. O., & Barry, C. L. (2014). Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999–2010. *JAMA Internal Medicine*, 4, 1–6. <http://dx.doi.org/10.1001/jamainternmed.2014.4005>.
- Belle-Isle, L., Walsh, Z., Callaway, R., Lucas, P., Capler, R., Kay, R., & Holtzman, S. (2014). Barriers to access for Canadians who use cannabis for therapeutic purposes. *International Journal of Drug Policy*, 25(4), 691–699. <http://dx.doi.org/10.1016/j.drugpo.2014.02.009>.
- Blessing, E. M., Steenkamp, M. M., Manzanares, J., & Marmar, C. R. (2015). Cannabidiol as a potential treatment for anxiety disorders. *Neurotherapeutics*, 12(4), 825–836. <http://dx.doi.org/10.1007/s13311-015-0387-1>.
- Bonn-Miller, M. O., Boden, M. T., Bucossi, M. M., & Babson, K. A. (2014). Self-reported cannabis use characteristics, patterns and helpfulness among medical cannabis users. *The American Journal of Drug and Alcohol Abuse*, 40(1), 23–30. <http://dx.doi.org/10.3109/00952990.2013.821477>.
- Bradford, A. C., & Bradford, W. D. (2016). Medical marijuana laws reduce prescription medication use in medicare part D. *Health Affairs*, 35(7), 1230–1236. <http://dx.doi.org/10.1377/hlthaff.2015.1661>.
- Brown, M. T., & Bussell, J. K. (2011). Medication adherence: WHO cares? *Mayo Clinic Proceedings*, 86(4), 304–314. <http://dx.doi.org/10.4065/mcp.2010.0575>.
- Carter, G. T., Weydt, P., Kyashna-Tocha, M., & Abrams, D. I. (2004). Medicinal cannabis: Rational guidelines for dosing. *IDrugs: The Investigational Drugs Journal*, 7(5), 464–470 Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/15154108>.
- Clark, C. (2013). The state of play. *International Journal of Play* 1–14. <http://dx.doi.org/10.1080/21594937.2013.853462>.
- Eysenbach, G. (2004). Improving the quality of web surveys: The checklist for reporting results of internet e-surveys (CHERRIES). *Journal of Medical Internet Research*, 6(3), e34+. <http://dx.doi.org/10.2196/jmir.6.3.e34>.
- Fischer, B., Murphy, Y., Kurdyak, P., Goldner, E., & Rehm, J. (2015). Medical marijuana programs—Why might they matter for public health and why should we better understand their impacts? *PMEDR*, 2, 53–56. <http://dx.doi.org/10.1016/j.pmedr.2014.12.006>.
- Fischer, B., Rehm, J., Goldman, B., & Popova, S. (2008). Non-medical use of prescription opioids and public health in Canada: An urgent call for research and interventions development. *Canadian Journal of Public Health*, 99(3), 182–184 Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/18615937>.
- Hager, M. (2016). Among veterans, opioid prescription requests down in step with rise in medical pot. *Globe and Mail* Retrieved from <http://www.theglobeandmail.com/news/national/among-veterans-opioid-prescription-requests-down-in-step-with-rise-in-medical-pot/article30285591/>.
- Hazekamp, A., Ware, M. A., Muller-Vahl, K., Abrams, D., & Grotenhermen, F. (2013). The medicinal use of cannabis and cannabinoids—An international cross-sectional survey on administration forms. *Journal of Psychoactive Drugs*, 45(3), 199–210. <http://dx.doi.org/10.1080/02791072.2013.805976>.
- Ingersoll, K. S., & Cohen, J. (2008). The impact of medication regimen factors on adherence to chronic treatment: A review of literature. *Journal of Behavioral Medicine*, 31(3), 213–224. <http://dx.doi.org/10.1007/s10865-007-9147-y>.
- Linge, R., Jiménez-Sánchez, L., Campa, L., Pilar-Cuellar, F., Vidal, R., Pazos, A., . . . Díaz, Á. (2015). Cannabidiol induces rapid-acting antidepressant-like effects and enhances cortical 5-HT/glutamate neurotransmission: Role of 5-HT1A receptors. *Neuropharmacology*, 103, 16–26. <http://dx.doi.org/10.1016/j.neuropharm.2015.12.017>.
- Lucas, P. (2012a). Cannabis as an adjunct to or substitute for opiates in the treatment of chronic pain. *Journal of Psychoactive Drugs*, 44(2), 125–133. <http://dx.doi.org/10.1080/02791072.2012.684624>.
- Lucas, P. (2012b). It can't hurt to ask: A patient-centered quality of service assessment of health Canada's medical cannabis policy and program. *Harm Reduction Journal*, 9(1), 2. <http://dx.doi.org/10.1186/1477-7517-9-2>.
- Lucas, P., Reiman, A., Earleywine, M., McGowan, S. K., Oleson, M., Coward, M. P., & Thomas, B. (2013). Cannabis as a substitute for alcohol and other drugs: A dispensary-based survey of substitution effect in Canadian medical cannabis patients. *Addiction Research & Theory*, 21(5), 435–442. <http://dx.doi.org/10.3109/16066359.2012.733465>.
- Lucas, P., Walsh, Z., Crosby, K., Callaway, R., Belle-Isle, L., Kay, R., . . . Holtzman, S. (2016). Substituting cannabis for prescription drugs, alcohol and other substances among medical cannabis patients: The impact of contextual factors. *Drug and Alcohol Review*, 35(3), 326–333. <http://dx.doi.org/10.1111/dar.12323>.
- Office of Medical Cannabis (2016). *MMPR market statistics, January–May*. Ottawa: Office of Medical Cannabis 2016.
- Ogborne, A. C., Smart, R. G., Weber, T., & Birchmore-Timney, C. (2000). Who is using cannabis as a medicine and why: An exploratory study. *Journal of Psychoactive Drugs*, 32(4), 435–443. <http://dx.doi.org/10.1080/02791072.2000.10400245>.
- Reiman, A. (2009). Cannabis as a substitute for alcohol and other drugs. *Harm Reduction Journal*, 6, 35. <http://dx.doi.org/10.1186/1477-7517-6-35>.
- Sawler, J., Stout, J. M., Gardner, K. M., Hudson, D., Vidmar, J., Butler, L., . . . Cockerham, C. (2015). The genetic structure of marijuana and hemp. *PLoS One*, 10(8), e0133292. <http://dx.doi.org/10.1371/journal.pone.0133292>.
- Sylvestre, D. L., Clements, B. J., & Malibu, Y. (2006). Cannabis use improves retention and virological outcomes in patients treated for hepatitis C. *European Journal of Gastroenterology & Hepatology*, 18(10), 1057–1063. <http://dx.doi.org/10.1097/01.meg.0000216934.22114.51>.
- Walsh, Z., Callaway, R., Belle-Isle, L., Capler, R., Kay, R., Lucas, P., & Holtzman, S. (2013). Cannabis for therapeutic purposes: Patient characteristics, access, and reasons for use. *International Journal of Drug Policy*, 24(6), 511–516. <http://dx.doi.org/10.1016/j.drugpo.2013.08.010>.
- Walsh, Z., Gonzalez, R., Crosby, K., Thiessen, M., Carroll, C., & Bonn-Miller, M. O. (2016). Medical cannabis and mental health: A guided systematic review. *Clinical Psychology Review* 15–29. <http://dx.doi.org/10.1016/j.cpr.2016.10.002>.
- Ware, M. A., Wang, T., Shapiro, S., Robinson, A., Ducruet, T., Huynh, T., . . . Collet, J. P. (2010). Smoked cannabis for chronic neuropathic pain: A randomized controlled trial. *Cmaj*, 182(14), 1–8. <http://dx.doi.org/10.1503/cmaj.091414>.
- Ware, M. A., Wang, T., Shapiro, S., & Collet, J.-P. (2015). Cannabis for the management of pain: Assessment of safety study (COMPASS). *The Journal of Pain* 1233–1242. <http://dx.doi.org/10.1016/j.jpain.2015.07.014>.



The medicinal use of cannabis in the UK: results of a nationwide survey

M. A. WARE,¹ H. ADAMS,² G. W. GUY²

Pain Centre,¹ McGill University Health Centre, Montreal, Canada; GW Pharmaceuticals plc,² Salisbury, UK

SUMMARY

The use of cannabis for medical purposes is a controversial but an important topic of public and scientific interest. We report on the results of a self-administered questionnaire study conducted in the United Kingdom between 1998 and 2002. The questionnaire consisted of 34 items and included demographic data, disease and medication use patterns and cannabis use profiles. Subjects were self-selected; 3663 questionnaires were distributed and 2969 were returned [1805 (60.9%) women, mean age 52.7 years (SD 12.7)]. Medicinal cannabis use was

reported by patients with chronic pain (25%), multiple sclerosis and depression (22% each), arthritis (21%) and neuropathy (19%). Medicinal cannabis use was associated with younger age, male gender and previous recreational use ($p < 0.001$). While caution must be exercised in interpreting these data, they point to the need for clinical studies of cannabis and cannabinoids with standardised and quality-controlled products.

Keywords: Cannabis; chronic diseases; epidemiology; pain; therapeutics

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INTRODUCTION

The potential use of cannabis and related derivatives (cannabinoids) for medical purposes is currently under intense scientific investigation. Research efforts are predominantly focused on exploring the cellular and neurophysiological effects of agonists and antagonists on endogenous cannabinoid receptors in animal models, and a novel endogenous cannabinoid pathway is being described with roles in movement, pain, appetite and cardiovascular control. This scientific knowledge is emerging at the same time as increasing numbers of patients' reports of the effective use of herbal cannabis. It is therefore plausible that patients using cannabis as a medicine may be exploiting this novel neurophysiological signalling system. Further information on the alleged effects of cannabis may guide the development of cannabis-based medicines for symptoms of chronic diseases.

Few data are available on the patterns and prevalence of the medicinal use of cannabis. A large number of case reports of effective medicinal cannabis use have been published in peer-reviewed journals, including central thalamic pain and dys-

tonia (1), proximal myotonic myopathy (2), familial Mediterranean fever (3) and multiple sclerosis (MS) (4). In a telephone survey of adults in 2508 households in Ontario, Canada, 49 people (1.9%) reported using cannabis for a medical reason in the past year, mainly for pain or nausea (5). Wide-ranging effects of cannabis are noted in large case series: 50 self-selected medicinal cannabis users reported use for a variety of conditions including HIV/AIDS-related problems, chronic pain, depression, anxiety, menstrual cramps, migraine and narcotic addiction, as well as everyday aches, pains, stresses and sleeping difficulties (6). In a survey of 53 UK and 59 US patients with MS, cannabis was reported to affect spasticity, chronic pain of extremities, acute paroxysmal phenomena, tremor, emotional dysfunction, anorexia/weight loss, fatigue states, double vision, sexual dysfunction, bowel and bladder dysfunctions, vision dimness, dysfunctions of walking and balance and memory loss (7). In a survey of 15 chronic pain patients who admitted to using cannabis medicinally, pain, sleep and mood were most frequently improved, while doses used were modest (8).

Several prospective studies among specific patient populations have now been published. In a survey of ambulatory patients with HIV/AIDS in three HIV clinics in eastern Canada, 35% reported current use of cannabis (9). This is higher than an estimated prevalence of 30% in British Columbia (10) and 15–23% in California (11,12). In a survey of 220 patients with chronic non-cancer pain, 10% reported continuing medicinal use (13). The prevalence of medical cannabis use among patients with MS has been estimated at 14% (14). Large population-based surveys are needed to further describe the characteristics of medicinal cannabis users and their reasons for use.

Correspondence to:

Dr Mark Ware, E19.145, Montreal General Hospital, 1650 Cedar Avenue, Montreal, Quebec, Canada H3G 1A4

Tel.: +1-514-934-8222

Fax: +1-514-934-8096

Email: mark.ware@muhc.mcgill.ca

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METHODS

A cross-sectional survey was conducted to collect data from self-selected medicinal cannabis users in the UK. Patients were identified by word of mouth and through patients' support groups. A questionnaire instrument was developed for postal distribution and self-administration. A stamped addressed envelope was provided to improve response rates. The questionnaire consisted of 34 items including binary (yes/no) responses, Likert scales and open-ended questions. Information collected included demographics (age and gender), disease and symptom status and patterns of cannabis use both medicinally and non-medicinally. Patients were asked to select their diseases and/or symptoms from a list, and space was provided for additional information. Disease and symptom information was accepted as reported by the patient in the questionnaire responses, and no attempt to validate these diagnoses was made.

Data were single-entered into a relational database (MICROSOFT ACCESS 2000). Missing data and outliers were excluded from the analysis; these accounted for less than 5% of the total responses for the variables of interest. Data were imported and analysed using a standard statistical package (STATA version 8, Houston, TX, USA). Categorical data were compared using Pearson's χ^2 -tests. Ordered categorical data were analysed using Mantel-Haenzel tests. Significance was set at the 95% level, and all tests were two sided. The database was registered with the Data Protection Act 1998.

RESULTS

Over the period 1998–2002, 3663 questionnaires were distributed, and 2969 were returned (81% response rate).

Demographic Information

The mean age of the 2969 subjects was 52.7 years (SD 12.7), of whom 1805 (60.7%) were female. MS was the most common disease, reported by 1753 subjects (59%), while 1280 reported neuropathy (43%), 1125 reported chronic pain (33%) and 777 reported arthritis (26%). There was considerable overlap among these conditions.

Cannabis Use Patterns

Ever Use of Cannabis for Medicinal Purposes. A total of 947 (31.9%) subjects reported ever having used cannabis for medical purposes. The remainder were assumed to be never users. The median duration of medicinal use among 616 subjects for whom the duration of use data were available was 4 years [interquartile range: (2–7)]. The demographic profile of medicinal cannabis users is summarised in Table 1, compared to the never users. Medical cannabis use was associated with male

Table 1 Characteristics of ever-medicinal cannabis users

Variable	Medicinal cannabis use				Total	p-Value
	Ever	%	Never	%		
Age (years)						<0.001
<45	395	55	325	45	720	
45–50	171	39	265	61	436	
50–59	274	30	643	70	917	
>60	104	14	620	86	724	
Gender						<0.001
Male	439	40	649	60	1088	
Female	508	30	1209	70	1717	
Non-medical cannabis use						<0.001
Yes	357	66	182	34	539	
No	575	28	1454	72	2029	

gender, younger age and non-medical use ($p < 0.001$ for all tests).

Continuing Use of Cannabis for Medicinal Purposes. Of those who had ever used cannabis medicinally, 543 (18.3% of total sample) persons reported continuing to use cannabis for medical purposes, while 403 (13.6%) said they no longer used it. The 30 diseases or symptoms for which continuing medical cannabis use was most common are summarised in Table 2, along with the median duration of use for each condition. As noted above, some subjects reported cannabis use for more than one purpose. Reasons given for no longer using cannabis for medical purposes are also summarised in Table 3.

Patterns of Cannabis Use

Frequency of Use. Patients were asked how many days per week they usually used cannabis for medicinal purposes. Of 946 responses, 333 (35%) used 6–7 days per week, 219 (23%) used 3–5 days per week, 139 (15%) used 1–2 days per week, 73 (8%) used less than 1 day per week and 182 (19%) reported 'other'.

Reasons for Trying Cannabis. When asked why they decided to try cannabis for medical purposes, 585 said it was because a friend, family member or acquaintance had suggested it, 519 said they read a book or article about cannabis, 177 said they had been prior users and found out 'by accident', 152 said their doctor had suggested it and 128 gave other reasons.

Modes of Administration. Smoking was the most common means of administration, reported by 777 (82%) of medical cannabis users. The modes of administration were: eating was reported by 406 (43%) subjects, tea by 267 (28%), sublingual spray by 20 (2%) and 118 (12%) used other means.

Amount of Cannabis Used. Nine hundred and sixteen subjects reported amounts of cannabis used for medical purposes. Of these, 18 used 10 or more grams per day, 60 used 5–9 g

Table 2 Thirty diseases and symptoms for which continuing cannabis use is most commonly reported

<i>Disease/symptom</i>	<i>Number</i>	<i>%</i>	<i>Median years of use (interquartile range)</i>
Multiple sclerosis	249	11.61	3 (2–6)
Neuropathy	239	11.14	4 (2–8)
Chronic pain	235	10.96	4 (2–9)
Depression	172	8.02	6 (3–10)
Arthritis	155	7.23	4 (2–8)
Gastrointestinal	84	3.92	5 (2–10)
Migraine	74	3.45	6 (3.5–15)
Allergy	62	2.89	3 (2–7)
Spinal pain	62	2.89	4 (2–9)
Asthma	53	2.47	4 (2–7)
Weight loss (unintended)	40	1.86	6 (2–13)
Spinal cord injury	39	1.82	7 (4–16)
Genitourinary	36	1.68	2 (2–5)
Chronic fatigue syndrome	27	1.26	4 (3–9)
Dystonia	27	1.26	2.5 (2–6)
Limited mobility	25	1.17	3 (2–6)
Epilepsy	24	1.12	4.5 (2.5–10)
Psychological	24	1.12	6.5 (3–17)
Fibromyalgia	23	1.07	5 (2–14)
Spinal disorder	22	1.03	5 (3–11)
Spinal surgery	22	1.03	6 (2–12)
Cardiovascular condition	21	0.98	4 (2–6)
Bone disorder	18	0.84	3 (2–6)
Spinal disc disorder	16	0.75	3 (2–10)
Spinal paralysis	16	0.75	9.5 (4.5–15)
Surgery	15	0.7	3.5 (2–16)
Visual impairment	15	0.7	5 (1–16)
Insomnia	14	0.65	4 (1–8)
Skin condition	14	0.65	3 (2–5)
Carcinoma	13	0.61	5 (4–6)
Other	309	14.4	n/a
Total	2145	100	

n/a, not applicable.

per day, 107 used 3–4 g per day, 249 used 1–2 g per day, 153 used several grams per week, 107 used several grams per month and 222 used only occasionally when needed.

Change in Amount Used. Seven hundred and seventy-seven subjects reported on whether the amounts of cannabis needed to control symptoms had changed over time since they had started; 54 said they needed much more, 171 needed a little more, 514 said it was about the same, 31 said they needed less and seven said they needed much less.

Table 3 Reasons for stopping medicinal cannabis

<i>Reason</i>	<i>Number of responses</i>	<i>% of number stopping</i>
Unable to find supply	207	7
Could not afford	169	5.7
Did not like side effects	40	1.3
Did not work	25	1
Did not like 'high'	20	0.7
Other	173	5.8

Perceived Effects of Cannabis

Overall Effectiveness. Of 948 reported users, 648 (68%) reported that cannabis made their symptoms overall much better, 256 (27%) said a little better, 36 (4%) said no difference and eight subjects said a little worse (four subjects) or much worse (four subjects).

Effectiveness Compared to Other Medications. When asked how cannabis compared to other medications overall, 412 of 916 subjects (45%) said it worked much better than prescribed medications, 261 (28%) said it was somewhat better and 45 (5%) said it was about the same; only 27 subjects said that prescription medicines worked better than cannabis (18 somewhat better and nine much better). One hundred and seventy-one (19%) subjects said it was impossible to tell.

Side Effects Compared to other Medications. When asked to compare the undesirable effects of cannabis to those of prescribed medicines, 872 subjects responded, of whom six found that cannabis produced much worse side effects, 23 found somewhat worse side effects and 54 said the side effects were about the same. Two hundred and sixty-four (30%) subjects stated that side effects of prescribed medicines were somewhat worse and 294 (34%) said they were much worse. Two hundred and thirty-one (26%) stated that it was impossible to tell.

Effects on Other Medication Use. Of the 909 subjects responding to this question, 374 stated that their use of cannabis had changed their use of other medications, while 521 said it had not. Fourteen were not coded.

Return of Symptoms on Stopping. Of the 876 subjects responding, 673 said their symptoms returned or got worse when they stopped using cannabis, and 203 denied any worsening on stopping cannabis.

Non-medicinal Cannabis Use. Five hundred and thirty-nine (18%) subjects reported ever having used cannabis for reasons not related to disease (assumed to mean non-medical use), while 2029 subjects stated that they had never used cannabis for non-medical purposes. Medicinal cannabis use was significantly associated with recreational use ($p < 0.001$) (Table 1).

DISCUSSION

To our knowledge, this is the most extensive survey of medical cannabis use among chronically ill patients conducted to date. Before any conclusions may be drawn, however, the potential limitations of the study must be addressed.

The sample of patients recruited for this study was not selected through any systematic procedure or by random recruitment. The questionnaire was distributed primarily by word of mouth to patients and patients' support groups, and

the high rate of response (81%) suggests that this was a highly motivated population. Therefore, there is potential for a strong selection bias to inflate the estimated of reported effectiveness of cannabis (assuming the responses reflect mainly 'successful' cannabis users) and to minimise the adverse effects. The subjects were chronically ill patients with a range of comorbid conditions, and the need for additional symptom relief may explain the self-reported on-going medical cannabis use prevalence of 18%. However, this is not out of the range of other prevalence surveys in MS (14%) (14) and chronic pain (10%) (13). However, because of the potential for bias, we caution against drawing any conclusions with respect to the efficacy of cannabis from this study. It is important, however, to recognise these results as contributing to our understanding of what the perceived effects of cannabis are among these subjects.

Most of the awareness of this study was achieved by word of mouth between patients, spread by patients putting notes about the project into their various newsletters/magazines, etc. MS patients have a large active patient support network in the UK and may have raised the awareness of this questionnaire study. This would have the effect of weighting the sample towards this population. There is a noticeable paucity of data from subjects with HIV/AIDS and cancer, populations which are also associated with therapeutic cannabis use. We believe that at the time of analysis, awareness of this questionnaire was not very high among the HIV/AIDS and cancer 'network groups'.

The presence of a significant selection bias may also have the effect of excluding cannabis non-responders, persons who have tried cannabis and for whom it has not been of any use. This is a difficult group to target, and only randomly selected large-scale surveys would be able to identify the extent of this. Such studies usually rely on postal distribution and often have low response rates. Detailed estimates of response to any medication are best captured in formal clinical trials.

In spite of these limitations, we believe that this survey is the best available assessment of current medical cannabis use in the UK. Some key messages emerge from the findings. Our study found that 68% of users had found cannabis to make symptoms overall much better and 27% a little better, suggesting that over 95% of the patients using cannabis had obtained some benefit from cannabis. In spite of this, about half of these subjects had not continued to use cannabis. The reasons for this are illuminating: the lack of supply or cost were more commonly reported as reasons for stopping compared to ineffectiveness or intolerable side effects. This lends support to ongoing efforts to make cannabis-based medicines available for research purposes and lends credence to changes in public policy on compassionate grounds.

The study has found that ever use of medicinal cannabis is significantly associated with young age, male gender and non-medical use. This relationship has been found in other surveys

(13) and may represent a general bias towards medical cannabis use in this population. Alternatively, the association may be explained by factors which make clinical response to cannabis more favourable in this population. It is known that males and females respond differently to cannabis (15), and younger age groups may be better able to find and use cannabis as more socially 'acceptable'. This may particularly be true of the recreational users who would more likely have discovered medical use by 'accident' (19% of ever-medical users).

Finally, recent randomised controlled clinical trials have pointed to potential therapeutic benefits of cannabinoids for patients with MS (16) and chronic neuropathic pain (17). This suggests that patients' reports of the effectiveness of cannabis should not be discounted as purely anecdotal, but rather could serve as a valid indicator of target diseases and symptoms for cannabinoid drug development.

In conclusion, we believe that this survey presents a broad picture of the current state of cannabis use for medical purposes in the UK. The extent of use and the reported effects lend support to the further development of safe and effective medicines based on cannabis.

Conflict of Interest Statements

MAW is conducting research on the safety and efficacy of cannabis for pain management and supported by the fonds de recherche en sante du Quebec and the Canadian Institutes of Health Research. GWG is the Chairman and CEO of GW Pharmaceuticals, a pharmaceutical company which is developing cannabis-based medicinal extracts. HAA is an employee of GW Pharmaceuticals.

Role of the Funding Source. GW Pharmaceuticals was responsible for designing and administering the questionnaire, setting up the database and entering the data. The extraction and analysis of data and the preliminary report were performed by the principal author (MAW) under a service agreement with GW Pharmaceuticals. This paper represents a final report on these data with the collaboration of all the authors.

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REFERENCES

- 1 Chatterjee A, Almahrezi A, Ware M, Fitzcharles MA. A dramatic response to inhaled cannabis in a woman with central thalamic pain and dystonia. *J Pain Symptom Manage* 2002; 24 (1): 4–6.
- 2 Hays H. Marijuana for the management of proximal myotonic myopathy. *J Pain Symptom Manage* 2001; 21 (4): 267–9.

- 3 Holdcroft A, Smith M, Jacklin A et al. Pain relief with oral cannabinoids in familial Mediterranean fever. *Anaesthesia* 1997; **52** (5): 483–6.
- 4 Hamann W, di Vadi PP. Analgesic effect of the cannabinoid analogue nabilone is not mediated by opioid receptors. *Lancet* 1999; **353**: 560.
- 5 Ogborne AC, Smart RG, Adlaf EM. Self-reported medical use of marijuana: a survey of the general population. *CMAJ* 2000; **162** (12): 1685–6.
- 6 Ogborne AC, Smart RG, Weber T, Birchmore-Timney C. Who is using cannabis as a medicine and why: an exploratory study. *J Psychoactive Drugs* 2000; **32** (4): 435–43.
- 7 Consroe P, Musty R, Rein J, Tillery W, Pertwee R. The perceived effects of smoked cannabis on patients with multiple sclerosis. *Eur Neurol* 1997; **38**: 44–8.
- 8 Ware MA, Gamsa A, Persson J, Fitzcharles MA. Cannabis for chronic pain: case series and implications for clinicians. *Pain Res Manag* 2002; **7** (2): 95–9.
- 9 Ware MA, Rueda S, Singer J, Kilby D. Cannabis use by persons living with HIV/AIDS: patterns and prevalence of use. *J Cannabis Ther* 2003; **3** (2): 3–15.
- 10 Braitstein P, Kendall T, Chan K et al. Mary-Jane and her patients: sociodemographic and clinical characteristics of HIV-positive individuals using medical marijuana and antiretroviral agents. *AIDS* 2001; **15** (4): 532–3.
- 11 Sidney S. Marijuana use in HIV-positive and AIDS patients: results of an anonymous mail survey. *J Cannabis Ther* 2001; **1** (3/4): 35–41.
- 12 Prentiss D, Power R, Balmas G, Tzuang G, Israelski DM. Patterns of marijuana use among patients with HIV/AIDS followed in a public health care setting. *J Acquir Immune Defic Syndr* 2004; **35** (1): 38–45.
- 13 Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ. Cannabis use for chronic non-cancer pain: results of a prospective survey. *Pain* 2003; **102** (1–2): 211–6.
- 14 Page SA, Verhoef MJ, Stebbins RA, Metz LM, Levy JC. Cannabis use as described by people with multiple sclerosis. *Can J Neurol Sci* 2003; **30** (3): 201–5.
- 15 Tseng AH, Craft RM. Sex differences in antinociceptive and motoric effects of cannabinoids. *Eur J Pharmacol* 2001; **430** (1): 41–7.
- 16 Zajicek J, Fox P, Sanders H et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003; **362** (9395): 1517–26.
- 17 Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. *JAMA* 2003; **290** (13): 1757–62.

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A survey of cannabis (marijuana) use and self-reported benefit in men with chronic prostatitis/chronic pelvic pain syndrome

Dean A. Tripp, PhD;* J. Curtis Nickel, MD, FRCSC;† Laura Katz, PhD;‡ Adrijana Krsmanovic, MSc;§ Mark A. Ware, MD, MRCP(UK), MSc;± Darcy Santor, PhD¶

*Departments of Psychology, Anesthesiology and Urology, Queen's University, Kingston, ON; †Department of Urology, Queen's University, Kingston, ON; ‡Psychology, Queen's University, Kingston, ON; §Alan Edwards Pain Management Unit, McGill University Health Centre, Montreal, QC; ¶School of Psychology, University of Ottawa, Ottawa, ON

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Abstract

Introduction: Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a chronic pelvic pain condition largely refractory to treatment. Cannabis (marijuana) use has been reported for a wide variety of chronic pain conditions, but no study has examined prevalence of cannabis use, symptom benefit or side effects, or frequency in CP/CPPS.

Methods: Participants were recruited from an outpatient CP/CPPS urology clinic (n = 98) and online through the Prostatitis Foundation website (n = 244). Participants completed questionnaires (demographics, CP/CPPS, depression, cannabis).

Results: The clinic sample included Canadian patients and the online sample included primarily American patients. Due to differences, groups were examined separately. Almost 50% of respondents reported using cannabis (clinic n = 49; online n = 89). Of the cannabis users, 36.8% of clinic and 75% of online respondents reported that it improved their symptoms. Most of the respondents (from the clinic and online groups) reported that cannabis improved their mood, pain, muscle spasms, and sleep. However, they did not note any improvements for weakness, fatigue, numbness, ambulation, and urination. Overall, the effectiveness of cannabis for CP/CPPS was "somewhat/very effective" (57% clinic; 63% online). There were no differences between side effects or choice of consumption and most reported using cannabis rarely.

Conclusions: These are the first estimates in men suffering from CP/CPPS and suggest that while cannabis use is prevalent, its medical use and benefit are unknown. This is an understudied area and the benefit or hazard for cannabis use awaits further study.

Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is characterized by pain in the perineum, pelvic, and suprapubic areas or the external genitalia with variable degrees of voiding or ejaculatory disturbances.^{1,2} The prevalence is about

7.1% (range: 2.2%–16%), with a 6.7% median.³ CP/CPPS symptoms do not routinely remit, with 66% of community-based samples experiencing symptoms 1 year later,⁴ and patients showing no changes in pain, disability, or catastrophizing over 2 years later.⁵ CP/CPPS etiology is unclear and medical treatments are largely ineffective.⁶ Medications (antimicrobials, alpha-blockers, anti-inflammatories), as well as phytotherapy, biofeedback, thermal therapies, and pelvic floor training have been examined⁷ and may provide mild benefit,⁶ but most men continue to experience chronic pain.

Physicians may use opioids to manage CP/CPPS pain, but their efficacy is limited and physicians fear tolerance, misuse, and side effects, such as nausea/vomiting or sedation.⁸ Chronic pain patients are turning to alternate forms of symptom relief, yet no research on this is available for CP/CPPS. Cannabis sativa has been used for pain and symptom relief for thousands of years. In Canada and several American states, patients use medical cannabis for severe intractable illnesses. As an addition to opioid treatment for chronic pain, vaporized cannabis results in pain reduction without altering plasma opioid levels.⁹ Moreover, 71% of the available randomized controlled studies concluded that cannabinoids were associated with pain relief, with low adverse effects, and good tolerance.¹⁰ Cannabis may be used in conjunction with or substitute for prescription opiates resulting in reduced opiate use.¹¹ Wide ranging types, quantities, and frequency of cannabis use for pain relief have been reported, with chronic non-cancer pain patients reporting previous use (15%) or current use (10%).¹²

We examined cannabis prevalence among men experiencing CP/CPPS-like symptoms from a tertiary care urology department and from an online group. Although previous work has not examined cannabis use in CP/CPPS, it was expected that use would echo previous pain studies.¹² We also solicited patient self-reports on the side effects or potential benefits, frequency, and indication of future cannabis use.

Methods

Participants/procedure

Identical online and outpatient surveys were administered to an online community-based sample and a tertiary care outpatient CP/CPPS clinic sample. All participants remained anonymous and received no financial compensation. Clinic patients were approached after their appointments and briefed about this Research Ethics Board-approved study. Interested participants then provided written consent and received a package (letter of information, debriefing form, questionnaires, postage-paid return envelope) to complete and mail back. The online sample was recruited through the Prostatitis Foundation.¹³ Participants were a self-selected “availability” sample from site visitors. All participants were required to read and write in English. All questionnaires were in English.

Measures

Demographics

Participants completed questions on demographics (age, CP/CPPS diagnosis, health problems, tobacco use, medication use).

Medical symptoms

The National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI)¹⁴ assessed prostatitis-like symptoms and their impact on daily life (pain, urinary symptoms, quality of life) providing a score range from 0 to 43. The self-administered NIH-CPSI provides a valid, psychometrically robust outcome measure.¹⁴ Confirmation of CP/CPPS cases was based on NIH-CPSI pain/discomfort in perineum and/or with ejaculation and NIH-CPSI total pain score of ≥ 4 (0–21), used in the community^{15–17} and in the general population¹⁸ studies.

Depression

The Patient Health Questionnaire 9 (PHQ-9)¹⁹ is a reliable and valid self-report measure using 9 items to assess depressive symptoms. An item sum was used for the indexation of depression.

Experience with cannabis

We used a 21-question descriptive survey on experience with cannabis; questions were binary (yes/no), multiple choice,

and rating scales. Questions included whether participants had ever used cannabis, the purpose of use, relief of pain/effects with use, potential side effects, usage frequency, and usage method.¹² Participants rated personal experience with different modes of delivery using Likert scale-style responses.

Data analysis

Scores were excluded if $>15\%$ of the items were missing on measures. Participants who provided $\geq 85\%$ of items on a particular measure had the missing items imputed using means replacement procedures.²⁰ As a check on generalizability, primary comparisons between the online and clinic data were computed for age and domains of NIH-CPSI (quality of life pain, urinary), and the PHQ-9. If outcomes differed significantly, online and clinical samples would be examined separately. Due to the exploratory nature, unadjusted t-tests and descriptive analyses (chi-square) were used to evaluate differences between cannabis users and non-users.

Results

The total sample of participants was comprised of an online self-reported CP/CPPS sample ($n = 376$) and a tertiary care outpatient CP/CPPS clinic sample ($n = 100$). Two participants were excluded from the clinic sample and 35% ($n = 132$) of the online sample was excluded due to incomplete data. In the end, we had 244 online and 98 clinic participants. Missing data pattern for the online group was random.

The online group was on average 10 years younger than the clinic group ($p < 0.001$), with an average age of 44.57 (standard deviation 13.96) for the full sample (Table 1). The clinic sample was Canadian and the online sample was primarily American.

The online group reported more depressive symptoms, pain, poorer quality of life, and worse symptom scores (Table 2). For the remaining analyses, samples were examined across groups. Most of clinic (63.3%) and online (79.1%) participants reported a score of 4 or above on prostatitis cut scores ($\chi^2 = 9.24$, $p = 0.013$). While the clinic and online groups did not differ in terms tobacco use ($\chi^2 = 1.17$, $p = 0.340$), the online group (63.1%) consumed more medication for pain, mood, sleep, or spasms than the clinic group (47.4%) ($\chi^2 = 7.00$, $p = 0.01$). There were no group differences when asked if they had ever used cannabis ($\chi^2 = 0.87$, $p = 0.390$) (yes 50% clinic, 44.3% online). Examining only those previously using, 36.8% clinic and 75% of the online groups reported that cannabis improved their symptoms ($\chi^2 = 7.63$, $p = 0.006$).

Participants were questioned whether cannabis use made their symptoms “worse/no better” to “slightly/much better” (Table 3). The large majority of online and half of clinic participants reported that cannabis improved their mood by a

Table 1. Sample demographics

	Online (n= 244)	Clinic (n = 98)
Age (years \pm SD)	42.04 (13.33)	51.56 (12.21)
Continent N (% of column total)		
North America	162 (66%)	
Canada	12 (7%)	98 (100%)
United States	150 (93%)	
South America	6 (2%)	
Europe	54 (22%)	
Australia	4 (2%)	
Asia	15 (6%)	
Africa (Egypt)	3 (1%)	

SD: standard deviation.

“slightly/much better” degree (Fisher’s exact test $p = 0.026$). Across both groups, cannabis’ effects made pain “slightly/much better” ($\chi^2 = 2.48$, $p = 0.619$), as with muscle spasms ($\chi^2 = 0.51$, $p = 0.474$), sleep ($\chi^2 = 0.54$, $p = 0.461$), and a borderline majority for nausea ($\chi^2 = 0.51$, $p = 0.474$). Also a minority of participants reported “slightly/much better” improvement in weakness ($\chi^2 = 3.11$, $p = 0.078$), fatigue ($\chi^2 = 3.40$, $p = 0.065$), numbness ($\chi^2 = 1.16$, $p = 0.281$), ambulating ($\chi^2 = 0.64$, $p = 0.423$), and urination (Fisher’s exact test $p = 0.432$). When asked on overall effectiveness of cannabis for CP/CPPS, most participants (57% clinic, 63% online) reported cannabis as “somewhat/very effective” ($\chi^2 = 7.89$, $p = 0.051$).

There was an even distribution of side effects reported by the groups, with most suggesting “none” to “mild” side effects from cannabis use (70.3% clinic, 70.8% online) ($\chi^2 = 0.05$, $p = 0.972$) (Table 4). Also, if offered a choice, participants reported similar preferences for cannabis method across groups ($\chi^2 = 1.99$, $p = 0.370$), but smoking was a leading choice. There were no differences when asked about the preferred form of cannabis they had used ($\chi^2 = 2.59$, $p = 0.274$), although most participants listed herbal option (buds, sinsemilla, hydroponic). In current cannabis users, frequency did not differ between groups ($\chi^2 = 0.27$, $p = 0.88$), with most respondents using “rarely” (73.3% clinic, 77.3% online).

Discussion

This is the first study to document the initial prevalence and patterns of cannabis use in men suffering from CP/CPPS from an outpatient urology clinic and online. Almost 50% of participants used cannabis and almost 3/4 reported using it for symptom relief. These figures are bigger than those in other studies.¹² The samples were treated as separate during analyses because the online group was younger, reported greater depression, pain, and diminished quality of life. Interestingly, while examining only those having used cannabis, fewer clinic respondents reported benefit compared to the online group. This almost doubling of the reported

Table 2. Psychological and NIH-CPSI differences between clinic and online participants

		N	Mean	SD	p value
Depressive symptoms	Clinic	92	7.15	6.66	<0.001
	Online	231	10.23	6.88	
NIH-CPSI pain domain	Clinic	98	9.04	5.79	<0.001
	Online	244	11.54	4.16	
NIH-CPSI urinary domain	Clinic	98	4.3061	3.43544	0.388
	Online	244	4.6475	2.92547	
NIH-CPSI QoL domain	Clinic	98	5.8061	3.53672	0.025
	Online	244	6.6680	2.04689	
NIH-CPSI total	Clinic	98	19.1531	11.13122	0.003
	Online	244	22.8566	7.23104	

NIH-CPSI: National Institutes of Health Chronic Prostatitis Symptom Inventory; SD: standard deviation; QoL: quality of life.

benefit by the online group may be related to symptom/disease severity differences in this study. The present data cannot describe factors underlying differences in benefit across groups, but this study is consistent with the suggestion that chronic pain is associated with lifetime marijuana use.²¹

Physicians should be aware and question patients on cannabis use. Despite a lack of information on the mechanisms of glycinergic cannabinoids for pain, cannabidiol, a major nonpsychoactive component of cannabis, suppressed chronic inflammatory pain in mice.²² Furthermore, the use of cannabis was not associated with analgesic tolerance in rats.²² It appears that cannabinoids’ anti-inflammatory action

Table 3. Cannabis illness-symptom effects across clinic and online participants

		“Worse/No Better” (n)	“Slightly/Much Better” (n)
Mood	Clinic	50.0% (12)	50.0% (12)
	Online	15.8 (3)	84.2% (16)
Pain	Clinic	33.3% (8)	66.7% (16)
	Online	26.3% (5)	73.7% (14)
Muscle Spasms	Clinic	47.8% (11)	52.2% (12)
	Online	36.8% (7)	63.2% (12)
Sleep	Clinic	25.0% (6)	75.0% (18)
	Online	15.8% (5)	84.2% (16)
Nausea	Clinic	58.3% (14)	41.7% (10)
	Online	47.4% (9)	52.6% (10)
Weakness	Clinic	82.6% (19)	17.4% (5)
	Online	57.9% (11)	42.1% (8)
Fatigue	Clinic	79.2% (19)	20.8% (5)
	Online	52.6% (10)	47.4% (9)
Numbness	Clinic	78.3% (18)	21.7% (5)
	Online	63.2% (12)	36.8% (7)
Ambulating	Clinic	79.2% (19)	20.8% (5)
	Online	68.4% (13)	31.6% (6)
Problems with bladder/urination	Clinic	87.5% (21)	12.5% (3)
	Online	73.7% (14)	26.3% (5)

Note. Numbers in BOLD represent the majority of respondents in the category row.

Table 4. Side effects, preferred choice, and form used for cannabis across groups

Cannabis side effects		None (n)	Mild (n)	Moderate-severe (n)
Preferred cannabis method for use if offered the choice	Clinic	37.0% (10)	33.3% (9)	29.6% (8)
	Online	39.3% (35)	31.5% (28)	29.2% (26)
		<i>Smoked</i>	<i>Sublingual spray/ vaporizer/inhaler</i>	<i>Rectal suppository/skin patch</i>
	Clinic	47.2% (17)	41.7% (15)	11.1% (4)
Cannabis form used	Online	61.1% (44)	29.2% (21)	9.7 (7)
		<i>Hashish</i>	<i>Herbal (Leaf and stem)</i>	<i>Herbal (Buds, sinsemilla, hydroponic)</i>
	Clinic	26.5% (9)	17.6% (6)	55.9% (19)
	Online	16.2% (12)	29.7% (22)	54.1% (40)

stimulates cannabinoid receptors.²³ However, contrasting results about cannabis side effects discouraged the authors for suggesting its chronic use for pain relief due to associated cognitive deficits and gastrointestinal toxicity.²³

The online group reported greater distress and NIH-CPSI symptoms, but both groups showed trends where most reported improved symptoms like mood, pain, muscle spasms and sleep. However, no improvements were in weakness, fatigue, numbness, or ambulation. Improved symptoms for some patients might reflect the shared effects that pain/muscle spasm can have in regard to improving sleep and ultimately mood. Current research shows that unresolved chronic pain, continuing disease, obesity, and sleeping problems predict the persistence of pain, while issues like mood are weakly associated.²⁴ Of other note, cannabis use was not helpful for urinary symptoms, which can be very bothersome in patients with CP/CPPS.

This survey showed that the side effects of cannabis appear minimal, with most patients reporting “none” to “mild” side effects. More detailed information on the amount of cannabis use, the types used (medical vs. other) would be important to provide a more detailed pattern of examining benefits. If offered a choice on how to use cannabis, participants reported smoking as the preferred methods – this is similar with other studies.²⁵ There were no differences by groups – the herbal form was endorsed by most respondents. In regard to current frequency of use, most participants reported using cannabis “rarely;” further study into usage patterns may shed some light on whether participants use cannabis primarily to manage pain flares or muscle spasms, or to aid with sleep. If usage is associated with intermittent pains, as flares, then that may reflect the rarity of reported use.

Our study has its limitations. This initial survey cannot qualify the benefits/risks of cannabis use in CP/CPPS, and simply suggests rates for further comparison. Sample size was an issue in some analyses because finer detail in questions, such as symptom benefit, had to be collapsed into 2 categories (“worse/no change” and “slightly/much better”) from original categories (“much worse,” “slightly worse,” “no change,” “slightly better,” “much better”). Larger samples

are necessary to gather more accurate patterns of use and benefit.

Although our samples were not randomized or stratified, they represent tertiary care outpatient males diagnosed with CP/CPPS, as well as community-based men with CP/CPPS-like symptoms. More online participants reported a prostatitis cut score. Perhaps the clinic men experienced reduced symptoms under the care of a specialist, but there was no opportunity to verify this in our study. Future research should also collect healthcare utilization and previous treatments prior to the onset of cannabis use. This data would allow contrasts and provide insight into medical comorbidities prior to cannabis use. It would also be interesting to examine the associations between psychological pre-cannabis use pain-associated comorbidities, like catastrophizing, and patterns of use.

Conclusion

This is the first study to examine and report on cannabis usage and benefit in participants with CP/CPPS from a tertiary care and community “availability” sample. The current data suggest that almost 50% of men with CP/CPPS-like symptoms have used cannabis in their lifetimes and that a minority of clinic patients versus most online participants reported cannabis benefit. Future research should examine larger representative samples to further document usage patterns, fuller CP/CPPS symptom benefit, and associated factors with usage in predictive models. The ultimate study would be a randomized controlled trial prospectively evaluating the efficacy and safety of cannabis compared to either placebo or an active comparator.

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This paper has been peer-reviewed.

References

- Krieger JN, Egan KJ, Ross SO, et al. Chronic pelvic pains represent the most prominent urogenital symptoms of 'chronic prostatitis'. *Urology* 1996;48:715-21. [http://dx.doi.org/10.1016/S0090-4295\(96\)00421-9](http://dx.doi.org/10.1016/S0090-4295(96)00421-9)
- Krieger JN, Nyberg L, Nickel JC. NIH Consensus definition and classification of prostatitis. *JAMA* 1999;282:236-7. <http://dx.doi.org/10.1001/jama.282.3.236>
- Nickel JC, Shoskes DA, Wagenlehner FME. Management of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS): The studies, the evidence and the impact. *World J Urol* 2013;31:747-53. <http://dx.doi.org/10.1007/s00345-013-1062-y>
- Nickel JC, Downey JA, Nickel KR, et al. Prostatitis-like symptoms: One year later. *BJU Int* 2002;90:678-81. <http://dx.doi.org/10.1046/j.1464-410X.2002.03007.x>
- Tripp DA, Nickel JC, Shoskes D, et al. A 2-year follow-up of quality of life, pain, and psychosocial factors in patients with chronic prostatitis/chronic pelvic pain syndrome and their spouses. *World J Urol* 2013;31:733-9. <http://dx.doi.org/10.1007/s00345-013-1067-6>
- Anothaisintawee T, Attia J, Nickel JC, et al. Management of chronic prostatitis/chronic pelvic pain syndrome: A systematic review and network meta-analysis. *JAMA* 2011;305:78-86. <http://dx.doi.org/10.1001/jama.2010.1913>
- Schaeffer AJ. Clinical practice. Chronic prostatitis and the chronic pelvic pain syndrome. *N Eng J Med* 2006;355:1690-8.
- Nickel JC. Opioids for chronic prostatitis and interstitial cystitis: Lessons learned from the 11th World Congress on Pain. *Urology* 2006;68:697-701. <http://dx.doi.org/10.1016/j.urol.2006.04.013>
- Abrams DI, Couey P, Shade SB, et al. Cannabinoid-opioid interaction in chronic pain. *Clin Pharmacol Ther* 2011;90:844-51. <http://dx.doi.org/10.1038/clpt.2011.188>
- Aggarwal SK. Cannabinergic pain medicine: A concise clinical primer and survey of randomized-controlled trial results. *Clin J Pain* 2013;29:162-71. <http://dx.doi.org/10.1097/AJP.0b013e31824c5e4c>
- Lucas P. Cannabis as an adjunct or substitute for opiates in the treatment of chronic pain. *J Psychoactive Drugs* 2012;44:125-33. <http://dx.doi.org/10.1080/02791072.2012.684624>
- Ware MA, Doyle CR, Woods R, et al. Cannabis use for chronic non-cancer pain: Results of prospective survey. *Pain* 2003;102:211-6. [http://dx.doi.org/10.1016/s0304-3959\(02\)00400-1](http://dx.doi.org/10.1016/s0304-3959(02)00400-1)
- Prostatitis Foundation. <http://www.prostatitis.org>. Accessed December 3, 2014.
- Litwin MS, McNaughton-Collins M, Fowler FJ Jr, et al. The National Institutes of Health chronic prostatitis symptom index: Development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. *J Urol* 1999;162:369-75. [http://dx.doi.org/10.1016/S0022-5347\(05\)68562-X](http://dx.doi.org/10.1016/S0022-5347(05)68562-X)
- Nickel JC, Downey J, Hunter D, et al. Prevalence of prostatitis-like symptoms in a population based study using the National Institutes of Health chronic prostatitis symptom index. *J Urol* 2001;165:842-5. [http://dx.doi.org/10.1016/S0022-5347\(05\)66541-X](http://dx.doi.org/10.1016/S0022-5347(05)66541-X)
- Tripp DA, Nickel JC, Ross S, et al. Prevalence, symptom impact and predictors of chronic prostatitis-like symptoms in Canadian males aged 16-19 years. *BJU Int* 2009;103:1080-4. <http://dx.doi.org/10.1111/j.1464-410X.2008.08157.x>
- Tripp DA, Nickel JC, Pikard JL, et al. Chronic Prostatitis-like symptoms in African males aged 16-19 years. *Can J Urol* 2012;19:6081-7.
- Hu JC, Link C, McNaughton Collins M, et al. The association of abuse and symptoms suggestive of chronic prostatitis/chronic pelvic pain syndrome: Results from the Boston Area Community Health Survey. *J Gen Intern Med* 2007;22:1532-7. <http://dx.doi.org/10.1007/s11606-007-0341-y>
- Spitzer R, Kroenke K, Williams J. Validation and utility of a self-report version of PRIME-MD. *JAMA* 1999;282:1737-44. <http://dx.doi.org/10.1001/jama.282.18.1737>
- Tabachnick BG, Fidell FS. *Using multivariate statistics*. 5th ed. Boston, MA: Pearson; 2007.
- Zvolensky MJ, Coughle JR, Bonn-Miller MO, et al. Chronic pain and marijuana use among a nationally representative sample of adults. *Am J Addict* 2011;20:538-42. <http://dx.doi.org/10.1111/j.1521-0391.2011.00176.x>
- Xiong W, Cui TX, Cheng KJ, et al. Cannabinoids suppress inflammatory and neuropathic pain by targeting alpha 3 receptors. *J Exp Med* 2012;209:1121-34. <http://dx.doi.org/10.1084/jem.20120242>
- Mulvihill MM, Nomura DK. Therapeutic potential of monoacylglycerol lipase inhibitors. *Life Sci* 2013;92:492-7. <http://dx.doi.org/10.1016/j.lfs.2012.10.025>
- Mundal I, Gräwe RW, Bjørngaard JH, et al. Prevalence and long-term predictors of persistent chronic widespread pain in the general population in an 11-year prospective study: The HUNT study. *BMC Musculoskelet Disord* 2014;15:213. <http://dx.doi.org/10.1186/1471-2474-15-213>
- Hazekamp A, Ware MA, Muller-Vahl KR, et al. The medicinal use of cannabis and cannabinoids—An international cross-sectional survey on administration forms. *J Psychoactive Drugs* 2013;45:199-210. <http://dx.doi.org/10.1080/02791072.2013.805976>

Correspondence: Dr. Dean A. Tripp, Department of Psychology, Queen's University, Kingston, ON K7L 3N6; dean.tripp@queensu.ca

Research

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Relief-oriented use of marijuana by teens

Joan L Bottorff*^{†1,2}, Joy L Johnson^{†2,3}, Barbara M Moffat^{†2} and Tamsin Mulvogue^{†2}

Address: ¹Centre for Healthy Living and Chronic Disease Prevention, University of British Columbia Okanagan, 3333 University Way, Kelowna, BC V1V 1V7, Canada, ²NEXUS Research Unit, University of British Columbia, 302-6190 Agronomy Road, Vancouver, BC V6T 1Z3, Canada and ³School of Nursing, University of British Columbia, 302-6190 Agronomy Road, Vancouver, BC V6T 1Z3, Canada

Email: Joan L Bottorff* - joan.bottorff@ubc.ca; Joy L Johnson - joy.johnson@ubc.ca; Barbara M Moffat - barb.moffat@nursing.ubc.ca; Tamsin Mulvogue - tamsin.mulvogue@mail.mcgill.ca

* Corresponding author †Equal contributors

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Abstract

Background: There are indications that marijuana is increasingly used to alleviate symptoms and for the treatment of a variety of medical conditions both physical and psychological. The purpose of this study was to describe the health concerns and problems that prompt some adolescents to use marijuana for therapeutic reasons, and their beliefs about the risks and benefits of the therapeutic use of marijuana.

Methods: As part of a larger ethnographic study of 63 adolescents who were regular marijuana users, we analyzed interviews conducted with 20 youth who self-identified as using marijuana to relieve or manage health problems.

Results: Thematic analysis revealed that these teens differentiated themselves from recreational users and positioned their use of marijuana for relief by emphasizing their inability to find other ways to deal with their health problems, the sophisticated ways in which they titrated their intake, and the benefits that they experienced. These teens used marijuana to gain relief from difficult feelings (including depression, anxiety and stress), sleep difficulties, problems with concentration and physical pain. Most were not overly concerned about the risks associated with using marijuana, maintaining that their use of marijuana was not 'in excess' and that their use fit into the realm of 'normal.'

Conclusion: Marijuana is perceived by some teens to be the only available alternative for teens experiencing difficult health problems when medical treatments have failed or when they lack access to appropriate health care.

Background

There is lively public debate surrounding the use of medical marijuana. While some remain sceptical about the therapeutic value of marijuana, there is a growing body of research that emphasizes its salutary effects. The literature points to the use of marijuana among adults to alleviate a

variety of symptoms including pain, nausea, muscle spasm, insomnia, anorexia and anxiety as well as the treatment of a variety of medical conditions that are both physical and psychological [1-5]. However, less is known about adolescents' use of marijuana for therapeutic purposes.

Background Literature

For individuals who set out to "feel better" through the use of marijuana, use has also been referred to as "self-medication," a hypothesis which posits that people do not misuse substances solely for the experience of being "high;" rather, they do so as a means of gaining relief from psychological and emotional pain [6]. In contrast to the adult literature on marijuana use where therapeutic use is linked to treatment of specific symptoms and illnesses, in the adolescent literature there is less clarity about how to define non-recreational uses of marijuana.

A motivationally-driven approach is one way that researchers have attempted to understand marijuana use among adolescents [7]. It is proposed that different reasons for using marijuana may shape patterns and contexts of use, which in turn may be associated with different problems related to use. Social motives for marijuana use, for example, have been associated with patterns of recreational use (e.g., sensation seeking). Coping motives have been used to classify adolescents using marijuana for non-recreation purposes. Differences have been observed among youth using marijuana for social and coping reasons that support the motives framework. In contrast to youth aged 16–24 years using marijuana for social reasons, users of the same age reporting coping motives have been observed to have lower mental health, higher psychopathology, more psychosocial distress and more stressful life events than non-cannabis-using youth [8].

Although there is a large body of literature related to recreational use of marijuana among adolescents [9,10] less is known about other motivations for the use of marijuana in this population. Several hypotheses have emerged related to non-recreational uses of marijuana among adolescents. The "self-medication hypothesis" [11-14] is most closely associated with the therapeutic use of marijuana. Instrumental use is another term applied to taking drugs for specific pharmacological effects of the substance rather than for pleasure or recreational purposes. For example, Glassner [15] examined the notion of instrumental drug use in a qualitative study of young drug users, and found that marijuana was used for its calming effects, to relieve tension, and to gain self-confidence. Further, support for a typology of drug related beliefs that included relief-oriented beliefs [16] was demonstrated in a study of cannabis use in a sample of 285 French high school students [17]. In this study, four 'positive' relief-oriented beliefs were identified related to how the substance creates relaxation and calms anxiety, reduces suffering, relieves boredom, and makes one feel better. The presence of relief-oriented beliefs was the only predictor of cannabis dependence.

Associations between marijuana and psychological problems have also lead researchers to consider other possible

explanations, including whether marijuana use may reinforce psychiatric symptoms or increase the risk of developing a psychiatric illness later in life [18-21]. A full understanding of marijuana use and its potential adverse effects, however, will require further research.

The trend toward the use of marijuana for therapeutic purposes among adults raises questions regarding how this may influence young people's use of marijuana for similar reasons. Recent studies suggest that adolescents are aware that marijuana is sometimes used to gain relief from physical and psychological pain [22-24]. Furthermore, there is evidence suggesting that adolescents may be using marijuana for reasons that are analogous to adults who use marijuana for therapeutic reasons. For example, young marijuana users with coping motives report more stressful life events (e.g., death of a family member or friend), personal injury and illness than socially motivated marijuana users and non-users [8]. There is also indirect evidence that adolescents with mental health conditions might be seeking relief through marijuana use. In a sample of 992 adolescents in drug treatment programs in four U.S. cities, more than half had at least one comorbid mental disorder. In total, 72.5% of these youth were dependent on marijuana [25]. Among youth entering outpatient treatment programs for cannabis use disorders, 76% were reported to have concurrent mental health conditions [26]. Finally, in a sample of homeless young people in the UK who used a variety of drugs including marijuana, participants were found to be self-medicating to deal with the stress and problems they encountered including depression, loneliness, and physical problems such as aches and pains [13].

As part of a larger study to understand the culture of frequent marijuana use among young people, we were struck by the extent to which some participants spontaneously described using marijuana to gain relief from symptoms. In order to develop these emergent findings, we conducted a focused ethnography in which we examined the ways in which youth use marijuana to seek relief.

Methods

This study was designed to understand and describe adolescents' experiences in using marijuana for therapeutic reasons, and explore how their constructions of these experiences are influenced by social norms. Compared to other types of ethnographic studies, focused ethnographies occur on a smaller scale and seek to examine a specific problem or phenomenon [27]. Typically, focused ethnographies are time-limited, involve a limited number of participants drawn from a specific population who have experience and understanding directly related to the area of inquiry, and are conducted through selected episodes of participant observation and/or interview [28]. In this focused ethnography, both in-depth interviews and participant observation were employed.

We drew data from a larger ethnographic study of frequent marijuana use among adolescents conducted in two rural and one urban location in British Columbia (BC), Canada. In the study communities, as is the case in much of BC, marijuana is readily accessible to youth despite the fact that it is illegal to grow, sell or possess. The use of marijuana for medical reasons is legally supported in Canada in limited circumstances; individuals meeting the criteria are provided with cannabis or given a license to grow a limited quantity for personal use.

Ethical approval for this study was obtained from the University Behavioral Research Ethics Board. Given the sensitivity of the topic and because we successfully argued that teens were able to provide consent for research participation, we did not require parental consent. As a courtesy, we provided the youth with a parent/guardian information letter which outlined the study's focus as pertaining to attitudes about marijuana use in general. Participants were told that they could take the letter home if they so chose. Prior to the interviews, written consent was obtained from the participants. Confidentiality was ensured at the outset and participants were informed that all identifying information would be removed from the data.

Sample

In the larger study, participants were recruited by means of information fliers posted at high schools which invited youth to share their "views on marijuana use and teens." Youth who expressed interest in participating were screened for eligibility by the research team. Eligibility criteria included being 13–18 years of age and reporting having smoked marijuana at least once in the previous week. In total, 63 young people participated in the study. Although many youth described "feeling better" after they smoked marijuana, a subset [$n = 20$] explicitly described experiences of using marijuana on a regular basis specifically to manage, reduce or eliminate unpleasant and uncomfortable feelings or other health problems. They constructed marijuana as a treatment for health problems, often suggesting it had significantly greater benefit than other medical treatments they had been offered. None of these students were legally provided with cannabis for medical treatment or given a licence to grow marijuana for medicinal use. Characteristics of this sub-set of participants are presented in Table 1. The majority of youth using marijuana for relief were male, and the average age of initiation of marijuana was 13 years of age. Youth in this subset were of diverse ethnic backgrounds. Most [$n = 12$] indicated that they were "Canadian" or "Caucasian;" More specifically, 2 participants identified as First Nations, 6 individuals were part First Nations, 3 of UK descent and 3 were of European background including Italian, Croatian, and Ukrainian. Compared to those who

Table 1: Description of participants who smoke marijuana for relief ($n = 20$)

<i>Gender</i>	
Female	7 (35%)
Male	13 (65%)
Age (years)	$X = 16$ yrs (range 14–18 yrs)
Age of initiation (years)	$X = 13$ yrs (range = 10–16 yrs)
Frequency of use (days)	$X = 2$ days/mo (range = 2–31 days/mo)
Number of times/day	1 – > 5 times/day
<i>Time of day of first use</i>	
Morning	4 (20%)
Afternoon	11 (55%)
Evening	5 (55%)
Marijuana use when alone	yes = 16 (80%)
<i>Reasons for use*</i>	
Depression	6
Stress/anxiety	12
Sleep problems	9
Focus/concentration	3
Physical pain	5

* some participants used marijuana for more than one reason

used marijuana for the purpose of relief, those recruited to this study who smoked marijuana for recreational purposes ($n = 43$) smoked marijuana less frequently (average of 11 days in the last 30 days) and used marijuana more often with others.

Data Collection

The primary source of data was in-depth, semi-structured interviews with youth to glean accounts of their experiences with marijuana. We used a short questionnaire prior to beginning the qualitative interview to collect demographic data and to assess history of marijuana use and current use. The questionnaire included items related to marijuana use including age of initiation, use in the last month, frequency and quit attempts. We also collected data on the time of day that individuals usually used marijuana.

The interviews were conducted using an interview guide. Broad discussion categories included: history and pattern of use, the reasons for their use, what they knew about marijuana, the sources of that information as well as contextual factors related to their use. Open-ended questions were posed in relation to each of these topics, as required during the interviews. Many of these youth were at ease when talking about their use of marijuana and needed little prompting. When youth described the use of marijuana to help them feel better, participants were asked to elaborate further on their experiences.

The tape-recorded interviews took place in privacy within the school setting and lasted from 1 to 2 hours. Participants were offered a \$20 honorarium. Field notes were used to record impressions of responses to the interview

and the interviewer's assessment of the quality of the interview. In addition, field notes were maintained to record pertinent observations within the school and in the larger community (e.g., noting school policies regarding marijuana use at school and the presence of graffiti related to marijuana in close proximity of the school; visiting favourite outdoor settings where some indicated that they preferred to smoke marijuana along with hemp shops where they purchased pipes and bongs and other paraphernalia).

Data Analysis

All data including transcribed interviews and field notes were reviewed several times by the research team paying close attention to young people's descriptions of experiences with the use of marijuana to address uncomfortable feelings or health problems, and the circumstances that surrounded this use. Close readings of the interviews by the investigative team involved highlighting potentially important comments, raising questions about the data, and identifying prominent dimensions of participants' experiences. During team meetings, interview data were discussed and emergent categories were identified to capture experiences related to marijuana use. These categories were organized into a coding framework and used to code the data. All coding was completed by one of the authors who completed a majority of the interviews (BMM). To code the data, we used [29] the NVivo software program designed for qualitative analysis of textual data. The program was also used to retrieve data coded under each category for a more nuanced analysis by the investigative team. Through reflective questioning of these data and detailed comparisons, themes were identified and discussed in team meetings.

Results

The Context of Using Marijuana for Relief

The teens situated their use of marijuana for relief of health problems in the context of difficult life events and illness experiences marked by a lack of supportive family networks, unexpected and sometimes traumatic losses of close friends or family members, and difficulties at school. Many indicated that they had few people to turn to help them; for some their parents were having difficulty coping with their own situations of unemployment, substance use, and marriage breakdowns and offered little support. Those living in households with a parent and step-parent had difficulty coping with unresolved feelings towards their estranged biological parent. Finally, several teens who made frequent moves with their families experienced social isolation at school and were subject to being bullied and teased.

Experiences with the medical system to address their health problems consistently fell short of the teens' expecta-

tations; their problems were either not taken seriously or the solutions offered were not helpful. For example, youth who reported they had been prescribed drugs such as Ritalin, Prozac or sleeping pills, stopped using them because they did not like how these drugs made them feel or found them ineffective. Despite visits to doctors, prescribed treatments and, for a few, hospitalizations, many of these teens perceived that they did not receive the help they needed from doctors.

A final contextual feature to these teens' lives were their observations of others' use of marijuana to deal with difficult circumstances or symptoms, including, in a few cases, parents and other significant adults in their life. For example, one young man reported that his mother was using marijuana while receiving cancer treatment. As he observed, "It helped her sleep and calmed her down." Others described how they were given advice from other teens about how marijuana could "help." Together these circumstances created a context where teens routinely turned to marijuana to manage physical and psychological problems in their lives. Marijuana was readily available, used by others in their network, and was perceived to provide an effective solution not offered to them from the medical system.

Regular Relief: Patterns of Using Marijuana for Persistent Problems

Most of the participants who consistently used marijuana for relief, smoked it when alone, often several times a day. For some, their day began and ended with using marijuana; they smoked before leaving home for school and prior to going to bed. Some indicated that they needed to smoke marijuana during the school day to manage symptoms, and when this occurred it was often in the company of friends. A few participants smoked marijuana for relief in adult company that included relatives and "older" friends who supported their need to use marijuana to manage symptoms.

There were two patterns of marijuana use for relief: intermittent and chronic. With intermittent use, youth routinely relied on marijuana to deal with short-term problems such as stressful situations or limited periods of physical pain. One 14 year old male described non-daily use occurring whenever he had a "really bad day." In the case of chronic use, daily marijuana was used for the relief of identified conditions such as depression, ADHD and to routinely settle at night or manage sleeplessness. Young people's descriptions of marijuana use for relief were imbued with language common to using pharmaceuticals. A number of these youth indicated how they carefully titrated their intake; others described their use as "moderate," involving a "few puffs," or just a "certain amount." Through experience, they had learned to hone

ways of using the right amount of marijuana to achieve a state of relief. As one male elaborated, he regulated his intake by mixing his marijuana with tobacco so as to get "just enough" marijuana to relieve regular states of agitation and high levels of stress. Along with skills at monitoring their intake of marijuana, these youth confidently shared in-depth knowledge of the strength and associated effects of different strains of marijuana.

Explaining the Need to Use Marijuana for Relief

The young people in the sub-sample were particularly articulate in describing their "need" to use marijuana. They were adamant and confident that marijuana provided relief from their health problems. The decision to smoke marijuana was stated in a straight forward fashion (e.g., "I started it to make myself feel better") and justified because they had a "reason for it." Participants also framed their marijuana use in a positive manner; in so doing, gave credence to the claim that this was the right course of action. As one girl elaborated on her daily use, "Pot helps me be me." Several described unpleasant physical sensations such as feeling "jittery" associated with the absence of marijuana. For these youth, regular marijuana use allowed them relief from these unpleasant symptoms so that they were able to feel "normal." One 18-year old male who used marijuana everyday indicated, "If anything, it makes you more normal." Of note, he had first started to use marijuana at the age of 13, and smoked it regularly for 5 years typically 4 times a day.

For these youth, the purpose of smoking marijuana was not specifically about getting high or stoned, nor was marijuana used for "pleasure." In fact, participants tended to differentiate their own use from peers who were recreational users who smoked marijuana when they were "partying" or "socializing." As one 16-year old male described his use, "I don't get a strong sense of euphoria, I just calm down a bit, that's just how it is for me." However, there were a few instances when female participants did smoke "to get high" for the purpose of "escaping reality," a strategy used to remove themselves temporarily from the challenging circumstances that accompanied their daily lives. The participants also distinguished themselves from the "stoner" stereotype, whose preferred activities were watching movies or listening to heavy metal music while smoking marijuana.

Some explanations of using of marijuana to feel better were further bolstered with a focus on use for described "health" reasons. As one 16-year old female indicated, her daily use of marijuana was "more of a health thing, than to get high." She reflected on her history of "mild depression" and her difficulties with antidepressants that had resulted in insomnia and a loss of appetite. She suggested that these health issues would re-surface in the absence of

marijuana, thereby providing solid rationale for her continued use of marijuana. One male situated his marijuana use within a perspective that medications are used to help deal with problems.

I bet you if I had never been put on Ritalin at a younger age, I might not have had the same opinion of drugs growing up, you know, because I was taught growing up that you take drugs to help you out with your problems, you know. [18 years, non-daily use]

Often, marijuana was compared to other substances in a way that suggested marijuana was the best option, further supporting ongoing use of marijuana for relief purposes. Some constructed marijuana as a "natural" substance that was preferable and considered "safer" than many pharmaceutical alternatives. One 14-year old female discovered that marijuana was a better option than dealing with the side effects of pharmaceuticals stating, "Well, my body, I have to be careful what pills I take. I have bad reactions to some medications. My body rejects it and I get really sick." Interestingly, one 18-year old who smoked twice a day on 21 days during the last month, went as far to describe himself as a "healthy marijuana user" adding, "It's not good for you, but then again, neither is MacDonald's and a lot of other things." The health claims in these descriptions served to explain the ongoing use of marijuana for relief.

Painful Lives: Types of Symptoms and Distress Requiring Relief

In the interviews the teens directly linked their use of marijuana with the management of difficult feelings (including depression, anxiety and stress), sleep problems, problems with concentration and physical pain. Each of these will be described in the following sections.

Difficult Feelings

Although some teens described using marijuana to deal with instances of being angry, experiencing a significant disappointment (e.g., with exam results), being afraid, or to forget the past, the most frequent uses were associated with dealing with depression, and managing stress and anxiety.

Depression

Six participants indicated they were using marijuana specifically to deal with depression and several others reported knowing teens that were doing the same. Dealing with difficult personal circumstances was a common theme for this group of teens and was linked to the loss of significant people in their lives, a family history of depression, financial worries at home, "fights" with parents, abuse, and too much "shit" in their lives. Several reported receiving treatment for depression in the form of antide-

pressants and counseling, sometimes over extended periods, yet with little relief. For others, these options were not available in part because "nobody wanted to listen" to them. As a last resort, these teens had opted to try smoking marijuana. In a relatively short time, marijuana helped them to feel better about themselves, happier and more like the person they "wanted to be" as well as alleviate other problems associated with depression (poor appetite, difficulty concentrating, poor sleep).

Not all participants agreed about the use of marijuana for depression. One 16-year old male used marijuana to deal with his unhappiness surrounding the conflict between his mother and father, and worried that he might be using pot too frequently. He reasoned that being happy all of the time was not natural, and that there was nothing wrong with being sad and confused sometimes. As a result, he tried to limit using marijuana to weekends with friends. Others believed that marijuana should only be used for certain types of depression because of the possibility of becoming more depressed by smoking pot:

I think it depends on the level of depression that you have. If it's like depressed because you are sick, then pot is helping you. It's making you happier. But if you're depressed about killing yourself, I don't think that it's a good idea to smoke pot just because it could bring you down more. It's hard to say, though, it's different for every person, right? That just how it makes me feel. [Female, 17 years, daily use]

Stress and anxiety

The use of marijuana to manage stress and anxiety was described by 12 teens in our sample. Dealing with bullying at school, heavy demands of school work, taxing shifts at work, and just "giving as much as you can" along side difficult relationships with parents or guardians, and receiving threats from neighbors all took its toll on these youth. For some, these experiences contributed to high levels of stress and anxiety, and for others uncomfortable levels of anger – both were difficult to manage. Although some had friends they could turn to, marijuana provided an additional source of stress relief that was ready at hand.

Lots of people know me, know I do pot and they think that I'm a pot head but really the thing they don't realize is that I have a reason for it. It's for my stress and an antidepressant. I get really upset. It [pot] helps me feel better about myself, because you know people don't do that [help me], like my friend [name] can, but nobody else can. [Female, 14 years, non-daily use]

There was general agreement among the teens that marijuana calmed them down, and helped them feel "not so nervous" and "not so uptight about everything." One teen

recognized, however, that despite the fact that marijuana could be a very effective stress reliever, it might not work for everyone:

Well as far as pot goes, the good thing is that it's definitely a stress reliever, hands down. I know lots of people who would be just a complete wreck if they weren't smoking pot but then there's also people who are a complete wreck because they do smoke pot, so it's kind of a hard thing. [Male, 16 years, non-daily use]

Sleep problems

Nine teens in our sample described using marijuana to help them sleep. The "trouble" they had with sleeping was a constant problem that many had experienced for years. One 16-year old, who also experienced mild depression, indicated that she "stopped sleeping for two years." Not only did the problem affect their school performance, but it was deeply disturbing to them. As another female described,

I have a really hard time sleeping. I can lay there for about four to five hours, just laying there. And I just finally had it, and I just feel like screaming I don't want to wake anyone up. So I go downstairs and ask my gran or my brother [for some marijuana] or I have a roach or two sitting around. [16 years, non-daily use]

Although one teen indicated that she had spoken to her mother about her problems sleeping, others indicated that the adults in their lives did not offer any support.

I have trouble going to sleep and waking up...My mum wanted to get the doctor to put me on sleeping pills but he said at such a young age it would cause like an addiction to them...I've had these problems since elementary school...I just, I can't go to sleep at night and then I like to sleep during the day. [Female, 14 years, non-daily use]

Many teens turned to pot and found almost immediate benefits in helping them sleep. Likened to a "magic sleeping pill" by one young male, the teens found it calmed their "busy minds," helped them relax and fall asleep quickly.

Focus/concentration

Three teens reported using marijuana to improve their concentration. They explained that they had difficulty focusing at school and that this affected their school performance. As one male explained:

Personally, I'm a very fast paced guy and my mind is always rushing, hard to gather my thoughts. I think a lot faster than I can speak. I get distracted very easily.

In social studies last year, I would talk and wouldn't do any work. But if I had just a little bit of pot, I could really focus my work. I could sit there and I'd work all day and finish everything and have no homework and be done by the end of class. [16 years, non-daily use]

These young people believed they could "think better" when they used marijuana because it allowed them to focus their thinking, and, slow it down in a way that was preferable. All suggested that these cognitive changes were linked to improved school performance. One teen, who self-identified as having "attention deficit, hyperactive disorder" shared the difficulties he experienced on Ritalin. He began smoking pot when he was 12 years of age and still on Ritalin.

Usually my mind is in over gear, right? I'm usually going about a mile a minute and my hands are moving way too fast, and I'm really fidgety. But if I have a puff of marijuana in a moderate use, by moderate I mean one to three to four puffs, depending on the quality....being toned down a bit I find really helps me....If I try to do homework at home without smoking pot, I just can't focus. I'll be looking at my schoolwork and for me with my ADHD this is how it's always been for me. Like school was just a constant story of this scenario before I smoked marijuana. [17 years, non-daily use]

Physical Pain

Five teens indicated they used marijuana to obtain pain relief, and several others shared similar stories about other youth. One male used marijuana to deal with pain associated with rehabilitation after a muscle injury, another used marijuana following an accident where he sustained 3rd degree burns and yet another because of plates in his back due to a car injury. Others suggested that marijuana reduced muscle pain after a hard day of skiing and helped with headaches, and that girls used marijuana for menstrual cramps. One 17-year old male used it daily and explained that marijuana "numbs your systems or senses [and] relaxes your muscles."

Considering the Risks of Using Marijuana for Relief

In spite of experiencing personal benefits from using marijuana for relief, some participants wrestled with their use of marijuana. One girl noted her own problematic use of marijuana that had quickly evolved into relying on it to deal with the regular stress in her life. As she pondered, she commented knowingly that it would be preferable to use it only when her stress level was "really" high.

I mean I started it, and I'm doing it for the wrong reasons...I think if I cut back and only did it when I was *really* stressed out or something, then, you know, really cut back, I think it would be okay. [14 years, non-daily use]

Although knowing that it was "harmful" to her body, she added that she found it difficult to quit using marijuana. Most youth were aware of the health consequences associated with marijuana use in general and their own use in particular. They noticed physical symptoms such as decreased stamina and shortness of breath with physical activities, while others worried about weakened immune systems and how it affected their energy level. Some recognized that they were addicted to marijuana. One male who had been using marijuana for six years framed it as something that he would address at a later date. "I'm trying to get through school and then worry about my dependency issue with marijuana."

Others noted that their marijuana use was linked to difficulties that they were having at school. One male concluded, "I think it brings marks down in one way and sometimes you don't understand things maybe as easily." Others recognized how their use had affected their memory. For a number of the participants, their knowledge of the risks of smoking marijuana was limited and, at times, incorrect. For example, as one 14-year old male who had started smoking marijuana in the past year to relieve muscle pain noted, "It's bad for your lungs, just it's 400 times lower than tobacco."

In what appeared to be an effort to minimize their use in the face of health risks, the teens emphasized that they were not using marijuana "in excess." One 18-year old summed up six years of using marijuana by saying, "I don't feel that I have a problem," adding that "it doesn't really have that many side effects." Some suggested that the benefits of smoking marijuana outweighed the risks. As noted, for those with difficulties sleeping at night, not being able to function the following day when sleep deprived was agonizing; marijuana use at night was preferable and provided a solution to that quandary. However, one male pondered both sides of his use of marijuana in dealing with his depression and was less optimistic:

Well, in some ways, it's helped me and some ways it hasn't. It's good when it's there, but when it's not, it kind of makes me sad. So it's hard like to try to keep up with staying happy all the time. [18 years, daily use]

Several participants made reference to the contradictions that they saw in their world regarding other licit substances and used that argument to make sense of and praise the benefits of marijuana over the risks.

And the thing is that if it's already used, they're already growing it for people that need it for medical help, then like why not.... Like no one has ever overdosed on marijuana, but people die everyday from alcohol, everyday from cigarettes and everyday from vast

amounts of things that the government has legalized, but they just won't legalize marijuana for some reason. It's never killed anyone, never really hurt anyone, it saves people's lives and they could make a good amount of money from it and drop crime rates, why don't they do it? [Male, 14 years, non-daily use]

Discussion

The findings of this study provide one of the first in-depth descriptions of youths' use of marijuana for non-recreational purposes, adding to the growing body of research on the use of drugs to self-medicate among young people. Teens involved in regular and long-term use of marijuana for relief constructed their use of marijuana as essential to feeling better or "normal" in situations where they perceived there were few other options available to them. Unlike the spontaneity typically involved in recreational use, these youth were thoughtful and prescriptive with their marijuana use – carefully monitoring and titrating their use to optimize its therapeutic effect. The findings also point to important contextual factors that further support youth's use of marijuana for relief that extend beyond the availability of marijuana and dominant discourses that construct marijuana as a natural product with medicinal properties.

Of key importance in the findings are the unmet health needs of these youth. Health issues such as depression, insomnia, and anxiety were significant problems that interfered with these youths' ability to function at school, maintain relationships with family and friends, and feel that they could live a normal life. The level of distress associated with these health concerns, along with the lack of effective interventions by health care providers and family members appeared to leave them with few alternatives. Researchers have reported that when adolescents in rural communities experience barriers to seeking health care, they think they can take care of the problems themselves [30]. Similarly, our study participants believed that their best option was to assume responsibility for treating their problems by using marijuana. Unpleasant side effects with prescribed medications and long, ineffective therapies resulted in little hope that the medical system could be counted on as beneficial. In contrast, marijuana provided these youth with immediate relief for a variety of health concerns. Nevertheless, the regular use of marijuana put youth at risk. Cannabis use has been identified as a risk factor for mental illness such as psychosis, schizophrenia [21,31,32] and psychiatric symptoms such as panic attacks [33]. Teens who smoked marijuana at least once per month in the past year were found to be three times more likely to have suicidal thoughts than non-users [34], and there is evidence that exposure to cannabis may worsen depression in youth [35]. Marijuana use among youth has also been associated with other sub-

stance use and school failure [36]. What is interesting is that the findings of this study suggest that youth have little awareness of some of these risks; rather, some are using marijuana to counteract these very problems (e.g., depression, school failure). Teens' perceptions that their health concerns were not addressed suggest that more attention is needed to assess these issues and ensure that other options are available to them. Parents and health care providers need to make a concerted effort to not only understand the pressures and influences on youth [37], but also gain a better understanding of the effect of youths' health problems on their ability to engage in healthy lifestyle choices.

Underlying problems related to youth health concerns also need to be addressed. In many situations, the participants' symptoms appeared to be directly related to their life circumstances. Along with the challenges inherent in being an adolescent in today's complex world, some teens were also trying to deal with significant losses (death of a close friend or family member), extremely difficult family relationships, disappointments with friends, school and sports, and a fragile family and peer support network. The risk of substance use increases substantially when youth are attempting to deal with these kinds of situations in isolation. Although marijuana provided the youth with temporary relief, the underlying situation often went unattended – leading the teens into a regular pattern of use. Appropriate guidance and targeted support from counselors and health care providers must be sensitive to meeting the needs of youth as they work through such situations and life altering events. In addition, adults working with youth must find better ways to talk with young people about how they are coping with their health issues, including their marijuana use. Based on the experiences of youth in this study, there is a wide range of support that may benefit youth including counseling, stress management, social skills training, anger management, study skills, pain management, and sleep hygiene. The youth in this study had minimal access to these types of resources.

The influence of the policy environment in Canada related to medical marijuana cannot be dismissed. The youth in this study were familiar with medical marijuana and its sanctioned use among those with serious illnesses; some knew individuals in their social network who were medical marijuana users. In addition, we acknowledge that the availability of marijuana in the study settings provided teens with opportunities to try marijuana to relieve symptoms. In locales where it is more difficult to access marijuana and penalties for possession of marijuana are harsh, teens with similar symptoms may use other approaches.

Despite presenting themselves as being sophisticated users of marijuana, with a rich knowledge of marijuana

acquired through direct experience, conversations and observations of others, the youth in our study did not appear to be well informed about the therapeutic use of marijuana. Targeted education for youth regarding the risks of marijuana and its appropriate use as a therapeutic agent is warranted, including the risks of legal sanctions. However, as Tupper [38] has suggested regarding drug education, fear-based approaches are unlikely to be effective when the reality of youths' observations and experiences suggest that few serious consequences stand in direct contrast to the "facts" teachers often provide. Alternative approaches are required that acknowledge the complexity of the issues that inform understandings of marijuana. Tupper suggests that drug education be framed using the metaphor of "drugs as tools" to allow "more nuanced understandings of the benefits and harms of drugs, depending on who is using them, in what circumstances, and for what purpose" (p. 235). This approach may be useful in education focused on marijuana.

This study was conducted in three locations in the province of British Columbia (BC) Canada and as such may not be generalized to other contexts. The province of BC is known for its illicit marijuana production [39]. And, in general the BC public is tolerant of marijuana use and support decriminalizing recreational use. In other contexts, teens might turn to other substances such as alcohol. The findings of this study provide a snapshot of these teens' use of marijuana. Further research is required to examine how this therapeutic use evolves over time.

Conclusion

In summary, this study highlights youths' efforts to address their health problems and their experiences in using marijuana for relief. Marijuana may be perceived by some teens to be the only available alternative for those experiencing difficult physical or emotional problems when medical treatments have failed or when they lack access to appropriate health care. As has been noted in other studies of substance use [40], understanding why adolescents use particular substances is key in developing appropriate educational and intervention programs.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JLB lead the data analysis, and conceptualized and participated in writing the manuscript. JLJ designed the larger study, participated in data analysis and the writing of the paper. BMM collected and analysed data, participated in writing of the manuscript. TM assisted with data management and contributed to the writing of the manuscript.

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References

- Bonn-Miller MO, Zvolensky MJ, Bernstein A: **Marijuana use motives: Concurrent relations to frequency of past 30-day use and anxiety sensitivity among young adult marijuana smokers.** *Addict Behav* 2007, **32**:49-62.
- Clark AJ, Ware MA, Yazer E, Murray TJ, Lynch ME: **Patterns of cannabis use among patients with multiple sclerosis.** *Neurology* 2004, **62**:2098-2100.
- Coomber R, Oliver M, Morris C: **Using cannabis therapeutically in the UK: A qualitative analysis.** *J Drug Issues* 2003, **2**:325-356.
- Ogborne AC, Smart RG, Adlaf EM: **Self-reported medical use of marijuana: A survey of the general population.** *CMAJ* 2000, **162**:1685-1686.
- Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ: **Cannabis use for chronic non-cancer pain: Results of a prospective study.** *Pain* 2003, **102**:211-216.
- Khantjian EJ: **The self-medication hypothesis of addictive disorders: Focus on heroin and cocaine dependence.** *Am J Psychiatry* 1985, **142**:1259-1264.
- Simons J, Correia CJ, Carey KB, Borsari BE: **Validating a five-factor marijuana motives measure: Relations with use, problems, and alcohol motives.** *Journal of Counseling Psychology* 1998, **45**:256-273.
- Brodbeck J, Matter M, Page J, Moggi F: **Motives for cannabis use as a moderator variable of distress among young adults.** *Addict Behav* 2007, **32**:1537-1545.
- May L, Katzenstein D: **Healthy youth development: Highlights from the 2003 adolescent health survey.** Vancouver, BC: McCreary Centre Society; 2004.
- Tjepkema M: **Use of cannabis and other illicit drugs.** *Health Rep* 2004, **15**:43-47.
- Bolton J, Cox B, Clara I, Sareen J: **Use of alcohol and drugs to self-medicate anxiety disorders in a nationally representative sample.** *J Nerv Ment Dis* 2006, **194**:818-825.
- Deykin EY, Levy JC, Wells V: **Adolescent depression, alcohol and drug abuse.** *Am J Public Health* 1987, **77**:178-182.
- Klee H, Reid P: **Drug use among the young homeless: Coping through self-medication.** *Health* 1998, **2**:115-134.
- Wilens TE, Adamson J, Sgambati S, Whitley J, Santry A, Monuteaux MC, Biederman J: **Do individuals with ADHD self-medicate with cigarettes and substances of abuse? Results from a controlled family study of ADHD.** *Am J Addict* 2007, **16**(Suppl 1):14-23.
- Glassner B: **Drugs in adolescent worlds: Burnouts to straights.** New York, NY, St. Martin's Press; 1987.
- Beck AT, Wright FD, Newman CF, Liese B: **Cognitive therapy of substance abuse.** New York, NY, Guildford Press; 1993.
- Chabrol H, Massot E, Mullet E: **Factor structure of cannabis related beliefs in adolescents.** *Addict Behav* 2004, **29**:929-933.
- Amar MB, Potvin S: **Cannabis and psychosis: What is the Link?** *J Psychoactive Drugs* 2007, **39**:131-142.
- Cohen M, Solowij N, Carr V: **Cannabis, cannabinoids and schizophrenia: integration of the evidence.** *Aust N Z J Psychiatry* 2008, **42**:357-368.
- Hall W, Degenhardt L: **Prevalence and correlates of cannabis use in developed and developing countries.** *Curr Opin Psychiatry* 2007, **20**:393-397.
- Moore THM, Zammit S, Lingford-Hughes A, Barnes TRE, Jones PB, Burke M, Lewis G: **Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review.** *Lancet* 2007, **370**:319-328.
- Menghrajani P, Klaue K, Dubois-Arber F, Michaud P: **Swiss adolescents' and adults' perceptions of cannabis use: A qualitative study.** *Health Educ Res* 2004, **20**:476-484.
- Plancherel B, Bolognini M, Stephan P, Laget J, Chinet L, Bernard M, Halfon O: **Adolescents' beliefs about marijuana use: A comparison of regular users, past users and never/occasional users.** *J Drug Educ* 2005, **35**:131-146.

24. Warner J, Room R, Adlaf EM: **Rules and limits in the use of marijuana among high-school students: The results of a qualitative study in Ontario.** *J Youth Stud* 1999, **2**:59-76.
25. Grella CE, Hser YI, Joshi V, Rounds-Bryant J: **Drug treatment outcomes for adolescents with comorbid mental and substance use disorders.** *J Nerv Ment Dis* 2001, **189**:384-392.
26. Tims FM, Dennis ML, Hamilton N, Buchan BJ, Diamond G, Funk R, Brantley LB: **Characteristics and problems of 600 adolescent cannabis abusers in outpatient treatment.** *Addiction* 2002, **97(Suppl 1)**:46-57.
27. Speziale HJS, Carpenter DR: *Qualitative research in nursing: Advancing the humanistic imperative* 4th edition. Philadelphia, PA, Lippincott Williams and Wilkins; 2006.
28. Muecke M: **On the evaluation of ethnographies.** In *Critical issues in qualitative research methods* Edited by: Morse J. Thousand Oaks, CA: Sage Publications; 1994:187-200.
29. QSR International Pty. Ltd: **NVivo Qualitative Data Analysis Software, Version 7.** 2006.
30. Elliott BA, Larson JT: **Adolescents in mid-sized and rural communities: Foregone care, perceived barriers, and risk factors.** *J Adolesc Health* 2004, **35**:303-309.
31. Fergusson DM, Horwood LJ, Ridder EM: **Tests of causal linkages between cannabis use and psychotic symptoms.** *Addiction* 2005, **100**:354-366.
32. Patton GC, Coffey C, Carlin JB, Degenhardt L, Lynskey M, Hall W: **Cannabis use and mental health in young people: cohort study.** *BMJ* 2002, **325(7374)**:1195-1198.
33. Zvolensky MJ, Bernstein A, Sachs-Ericsson N, Schmidt NB, Buckner JD, Bonn-Miller MO: **Lifetime associations between cannabis, use, abuse, and dependence and panic attacks in a representative sample.** *J Psychiatr Res* 2006, **40**:477-486.
34. Greenblatt J: **Substance Abuse and Mental Health Services Administration. Adolescent self-reported behaviors and their association with marijuana use 1998** [<http://www.oas.samhsa.gov/treatan/treana17.htm>].
35. Office of National Drug Control Policy, Executive Office of the President: *Teen marijuana use worsens depression: An analysis of recent data shows "self-medicating" could actually make things worse* Washington, DC, Office of National Drug Control Policy, Executive Office of the President; 2008.
36. Health Canada: *Health Canada's marihuana supply* Ottawa, ON: Health Canada; 2005.
37. Substance Abuse and Mental Health Services Administration: *2006 National Survey on Drug Use and Health 2007* [<http://www.oas.samhsa.gov/nsduh/2k6nsduh/2k6results.pdf>].
38. Tupper KW: **Drugs, discourses and education: A critical discourse analysis of a high school drug education text.** *Discourse: Studies in the Cultural Politics of Education* 2008, **29**:223-238.
39. Mulgrew I: *Bud Inc.: Inside Canada's marijuana industry* Toronto, ON, Random House; 2005.
40. Boys A, Marsden J, Strang J: **Understanding reasons for drug use amongst young people: a functional perspective.** *Health Educ Res* 2001, **16**:457-469.

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Who is Using Cannabis as a Medicine and Why: An Exploratory Study[†]

Alan C. Ogborne, Ph.D.*; Reginald G. Smart, Ph.D.*;
Timothy Weber, B.A.** & Carol Birchmore-Timney, M.A.**

Abstract—This article reports on an exploratory study of medical cannabis users. Interviews were completed with 50 self-identified medical cannabis users recruited through notices in newspapers and on bulletin boards. They reported using cannabis for a variety of conditions including HIV-AIDS-related problems, chronic pain, depression, anxiety, menstrual cramps, migraine, narcotic addiction as well as everyday aches, pains, stresses and sleeping difficulties. A majority also used cannabis for recreational purposes, and many were longer-term cannabis users. However, there were some notable exceptions. Almost all smoked cannabis and many did so two to three times a day. Few admitted negative experiences with cannabis, although some problems evident to the researchers were not clearly admitted. Those who told their doctors about their medical cannabis use found doctors noncommittal or supportive. The results raise questions about the definition of medical cannabis use and about policies that might be developed to accommodate such use. Limitations of the study are noted and further research suggested. Research priorities include population surveys, studies involving larger, more representative samples of medical cannabis users and studies of medical cannabis use among people with HIV-AIDS.

Keywords—cannabis, HIV/AIDs, medical marijuana, self medication

Cannabis has a long history of use as a medicine, and during the 19th century extracts of cannabis were recommended by respected physicians for a wide range of medical conditions (Grinspoon & Bakalar 1997). Cannabis was considered to have analgesic, sedative, anti-inflammatory, antispasmodic, anti-asthmatic and anticonvulsant properties and promoted for the treatment of tetanus, cholera, pruritis, uterine dysfunction, labor and menstrual pains, gout, asthma, neuralgia, rheumatism, convulsions and

depression. Early in the 20th century the use of cannabis fell out of favor with the medical profession due to the discovery of newer, more stable and effective drugs. A synthetic form of THC (dronabinol or marinol) has since been developed for the treatment of nausea associated with chemotherapy and AIDS-related anorexia. However, until recently, cannabis has mainly been used illegally as a recreational drug with the intention of getting high rather than treating medical conditions.

Anecdotal and journalistic evidence indicating that cannabis is regaining popularity as a medicine has been accumulating since the 1970s. Personal testimonials from users and statements by lobbyists and some physicians have indicated that cannabis is used by people suffering from glaucoma, multiple sclerosis, epilepsy, mood disorders, and other disorders that cause pain, muscular tension or spasms (Campbell 1996). One study of people using a buyers' club

[†]The views expressed in this paper are those of the authors and do not necessarily reflect those of the Centre for Addiction and Mental Health

*Senior Scientist, Centre for Addiction and Mental Health, London, Ontario, Canada.

**Research Associate, Centre for Addiction and Mental Health, London, Ontario, Canada.

Please address correspondence and reprint requests to Alan C. Ogborne, Ph.D., Addiction Research Foundation, UWO Research Park, 100 Collip Circle, Suite 200, London, Ontario, Canada N6G 4X8. E-mail: ogborne@julian.uwo.ca

in California showed that many were using cannabis to treat AIDS-related symptoms or for a variety of chronic pain, neurological and psychiatric disorders (Harris, Mendelson & Jones 1998).

There are two published studies of medical cannabis use among people with HIV/AIDS. The first was a survey conducted during 1993/94 that involved patients of an AIDS clinic in Alabama (Dansak 1997). Of the 72 patients interviewed, 33 (46%) were currently using cannabis and almost all had used it before the onset of AIDS/HIV. Most current users had used cannabis for medical reasons as it had beneficial effects on gastrointestinal conditions such as nausea, vomiting, indigestion and appetite. A few also noted that cannabis helped alleviate depression and two noted that it reduced anxiety.

The second study of medical cannabis use by persons with HIV/AIDS was conducted in Hawaii (Wesner 1996) through an AIDS Newsletter. It reached 374 persons affected with AIDS or HIV but only 35% responded, and it is not clear whether respondents were more likely to have used cannabis than nonrespondents. Of those who did respond, 36.9% had used cannabis as a therapy for AIDS symptoms; of those who had also used prescription anti-emetics, 80% preferred cannabis. A third of those who had used cannabis medically had not discussed this with their doctors.

There are no published surveys of medical cannabis use among people suffering from chemotherapy-induced nausea, multiple sclerosis, epilepsy or other physical conditions for which cannabis is said to be helpful. However, several surveys have shown that cannabis use is common among psychiatric patients who often seem to use cannabis to medicate psychiatric symptoms (Beesley & Russell 1997; Rohnaar & Timmerman 1997; Mathers et al. 1991; Blackwell, Beresford & Lambert 1987).

The prevalence of medical cannabis use is not known except in Ontario, where the results from a province-wide survey of adults aged 18 and over indicate that about 2% had intentionally used cannabis for self-defined medical reasons at least once in the past year. This represents 7.6% of those who had ever used cannabis and 22% of those who had used cannabis in the last year. No comparable figures are available from other Canadian provinces or from other countries. The latest national drug survey in Canada was in 1994 and this showed that 7.6% of the adult population had used cannabis in the past year (Smart & Ogborne 2000). However, no questions about medical cannabis use were included.

The medical use of cannabis raises new and important medical, social policy and legal issues concerning the rights of people to use an illegal substance for medical reasons. In the United States and in Canada there is considerable public support for the medical use of cannabis and for the rights of physicians to recommend cannabis to people who might benefit from it (Lindesmith Centre 1998; Angus Reid Group

1997). Attempts have also been made to establish buyers' clubs to provide cannabis to those with legitimate medical needs, and several recent court rulings have been in favor of the rights of sick people to use cannabis for medical reasons. More information is therefore needed on the nature and extent of medical cannabis use and on motivations, characteristics and experiences of those involved. This is especially so because cannabis is used medically by some of the most vulnerable and sickest people. This article reports a study that explores why people use cannabis for medical reasons, the effects they get, their methods and patterns of use, their experiences with physicians and their encounters with the law. It provides an analysis of interviews with 50 cannabis users in Toronto.¹ These interviews were conducted to (1) assess the feasibility of a larger study involving medical cannabis users and (2) explore opinions and practices concerning the medical use of cannabis. Implications for further research and for social policy are considered in the discussion.

METHODS

Those interviewed were recruited mostly through notices placed in newspapers and on bulletin boards at the Addiction Research Foundation, downtown bookstores, grocery stores, restaurants, and laundromats, AIDS clinics and drop-in centres and an informal buyers' club. These notices invited those who had ever used cannabis for medical reasons to share their experiences in a confidential interview. A few respondents (less than five) were also recruited through contacts with professionals and through the use of snowball sampling. Those who called in response to information about the study and who said that they used cannabis for medical conditions were invited for an interview. Most interviews were conducted at the Addiction Research Foundation. Others were conducted in respondents' homes, at a drop-in centre, or a restaurant; two interviews were conducted by telephone. All those interviewed were paid \$10. All interview questions were open-ended and encompassed a range of topics. In this article, the focus will be on: (1) reasons for the medical use of cannabis; (2) other attempts to treat the conditions for which cannabis was used; (3) routes to cannabis use; (4) methods of use; (5) patterns and amounts of use; (6) sources of supply; (7) negative experiences with cannabis; and (8) experiences with physicians.

RESULTS

Fifty (50) individuals were interviewed over a six-month period. About 70 others inquired about the study but could not be contacted. Twenty others did not show up for interviews. Of the 50 people interviewed 33 (66%) were male. The average age was 38, with a range from 26 to 57.

TABLE 1
Main Medical Condition for which Cannabis Use was Reported: Number of Respondents

HIV/AIDS-related symptoms	11
Chronic or recurrent pain due to injury or of unknown origin	7
Clinical depression*	6
Chronic stress or anxiety**	3
Narcotic addiction	2
Menstrual cramps	2
Anorexia/bulimia	2
Asthma	2
Migraine	2
Multiple self-diagnosed minor ailments and everyday stress**	2
Epilepsy	2
Lupus	1
Graves disease	1
Vocal Tourette's Syndrome	1
Multiple sclerosis	1
Retinitis pigmentosa (night blindness)	1
Chemotherapy-induced loss of appetite	1
Unexplained nausea	1
Hepatitis	1
Crohn's Disease	1
Arthritis	1

*For which they had received medical or psychiatric treatment (not noted in text).

**Did not seek treatment.

Medical Reasons Reported for Cannabis Use

Table 1 shows the conditions for which respondents said they used cannabis. The majority (n=34) reported using cannabis to treat symptoms of organic illnesses or to treat pains due to accidents or unknown causes. The most common organic illness was HIV/AIDS (n=11). Others (n=9) said they used cannabis for serious psychological problems (clinical depression or chronic anxiety), anorexia (n=2) or symptoms related to narcotic addiction (craving and methadone-related nausea). One person claimed to use cannabis to treat chronic but unexplained nausea. Finally, two reported using cannabis to treat minor medical conditions and cope with everyday stresses.

A wide range of symptoms or conditions were reportedly relieved by cannabis including difficulty sleeping, physical pain, loss of appetite, nausea, seizures, tics and muscle spasms, craving for narcotics, loss of energy, depression and anxiety. Table 2 shows the frequency with which specific symptoms were mentioned. The total number of symptoms exceeds the number of respondents because many reported using cannabis for two or more symptoms or conditions. Typically nausea and loss of appetite were mentioned together as were depression and anxiety.

The reported reasons for taking cannabis varied greatly:

Its mostly for spasms. I use it for relaxing . . . I get a lot of pain running all down my neck. . . . I get a lot of spasms coz of the HIV . . . It [cannabis] helps because it relaxes me and gets rid of the muscle pains in my neck. (male with HIV).²

I can see clearer . . . a little sharper. . . . Sometimes my eyes start . . . pulsating . . . itchiness and stuff and after I do one of those [smoke a joint] . . . no problem. (male with retinitis).

If I have no marijuana I'm no good for nobody. . . . But the moment I smoke a joint I've got self-esteem, it makes me feel good. (male with HIV).

I could not control my focus . . . I have double vision . . . it [cannabis] helps me. . . . The condition of my eyes has improved and he [the doctor] could see this because he made me undergo tests. (male with eye problems related to Graves disease).

. . . to increase my appetite . . . my metabolism burns very fast. Can't gain an ounce . . . can't even maintain weight unless I eat five, six times a day. Can't bring myself to do that unless I smoke a couple of joints. (male with anorexia).

I have really excruciating pain and I find it [cannabis] helps. (female with chronic back pain).

He is currently using medical marijuana for pain relief for lupus and vascularities associated with lupus; capillaries break and it results in sores that are quite painful. A secondary use is to relieve nausea and pain associated with the drugs for lupus. (Interviewer notes on male with lupus).

If I'm seizing I will get someone . . . [and] they'll come by with a couple of joints and . . . take a puff . . . then in a few seconds or a few minutes I got no seizure problems whatever. It's amazing how it works. (male with epilepsy).

I take 30 pills a day . . . I feel nauseated most of the time . . . marijuana takes care of the nausea . . . prescriptions from the doctor . . . don't work as well. (male with HIV).

TABLE 2
Number of Respondents with Symptoms Reported to be Relieved with the Use of Cannabis*

Problems sleeping	28
Loss of appetite	21
Nausea or pain (including menstrual cramps and headaches)	14
Depression	12
Anxiety/tension	11
Ticks and muscular spasms	10
Seizures	4
Loss of energy	3**
Difficulty breathing (asthma related)	2
Craving for heroin	2
Anger	1
Eye irritation and double vision (in Graves Disease)	1

*Number of symptoms exceeds number of respondents because some respondents reported two or more symptoms that were relieved by cannabis.

**Includes one person who developed seizures following the onset of HIV infection.

... if you're feeling really, really bad some days ... eh maybe escape isn't the right word because it's a drug but it gives you some relief to make that go away for a while ... if I am really bad I don't take the Tylenol 3. I would rather take a few tokes. (female with multiple sclerosis).

It's an unexplained nausea ... to the point of vomiting ... I won't eat for three to four days and then I'll still be vomiting like dry heaves. I just like a little bit [of cannabis] ... it's just to make it go away ... (female with nausea).

To induce my appetite because I'm on methadone ... I lost about 25 pounds cause of it ... suppresses your appetite but it also make you nauseous ... I wasn't eating at all for three days at a time ... so I started smoking ... it worked for the nausea when I was pregnant ... and it helps me sleep. (female with nausea and narcotic addiction).

I find [prior to menstruation] my body goes through ... aches and pains and back pains ... and when I smoke marijuana it tends to relieve it ... I'm able to function ... as opposed to going and taking a Midol or going to my family physician ... for a synthetic prescription. (female with menstrual cramps).

I started smoking because that was the only way I could eat and function. Otherwise I had to stay in bed ... [I] was so sick. But when I smoked a joint I can clean the house ... eat ... but as soon as it passed I have to go back to bed. (female with HIV).

Bulimia, anxiety, depression ... what it does [cannabis] is it calms down my system so that I can eat and think rationally. I get all my stuff down and then it's time for bed. (female with anorexia).

[Cannabis] helps me with my nerves and sometimes with pain ... I don't know if I could ... live and be functional without it [cannabis] unless I got something under a doctor's care but because of my liver any pills are bad for me. (female with anxiety and hepatitis).

I use it [cannabis] to alleviate cravings for heroin. It helps me get through the day without using heroin. (male receiving methadone).

Nausea, which you suffer from a lot when you have Crohn's, [also] loss of appetite ... lot of pain it would help with that. Also ... with Crohn's you'd have a lot of like spasms of your stomach or your bowel inside and it would help with that. (male with Crohn's disease).

If I've got a boardroom meeting let's say at 3:00 today, at 1:00 I'll take a "butt" ... I'm very ... lucid. (male with Tourette's Syndrome).

Treatments Other than Cannabis Tried for Main Conditions and Symptoms

Other attempts to treat the symptoms and conditions that motivated self medication with cannabis were quite variable. In some cases it was not clear that alternatives to cannabis had been tried. However, in other cases cannabis was described as superior to other, more conventional, treatments:

[I've tried] Dilantin and phenobarbital but they were not controlling the seizures. ... I've not used any other medication (except cannabis) since 1971. (male with epilepsy).

Two specialists ... gave me pills ... but they didn't make a noticeable difference. ... I've tried health food stuff ... it just takes a little bit [of cannabis] ... to make it [nausea] go away. (female with chronic nausea).

So ... I tried ... Prozac. It did not help me ... it made me a different person ... very introverted ... withdrawn. (female with migraines and insomnia).

I was taking tons of medication ... a major dose of Anafranil [an antidepressant] and ... Rivatrol [an anticonvulsant] and ... they were getting me very lethargic and laid back ... what was happening was it was getting me so stoned and so happy ... my tics didn't go away ... [but] I couldn't give a hoot and hinny ... (male with Tourette's Syndrome)

They [doctors] gave me Tylenol 3s and they made me a bit groggy. ... I wanted to work ... I noticed that when I took a

bit of marijuana it alleviated the symptoms and allowed me to function normally. (male with repetitive strain injury).

I was on Serax [a sedative] once for almost a year but I found that taking Serax made me sick. It made my stomach feel real weird. So I discontinued it... marijuana makes you feel strange but it's a good kinda strange . . . it's not the kinda stone where you're walking around and your head feels like it's 15 miles high. (male with HIV).

I tried different pain killers and at first they seemed to be okay but . . . they stopped writing prescriptions for me. I found it [the marijuana] helped. It made me motivated and gave me energy and kept me active. (female with back pain).

I was taking Valium, diazepam . . . like I took it for like three years and then I started smoking marijuana . . . I didn't have the same feelings I had when I was taking the Valium. I felt more calm, more relaxed. . . . It was able to open my appetite to eat. (male suffering from depression).

Well, I suffer from depression and when you're really, really, really depressed a joint works a lot better. . . . I've tried all the antidepressants, like all of them and I've just given up on it. (male with depression).

Cannabis was, however, also sometimes used in combination with drug treatments that respondents found helpful.

I'm a chronic asthmatic, So . . . I'm using it [cannabis] in combination with . . . Beclavent which is a long-term steroid and occasional use of Ventolin, an immediate release asthmatic drug, just for when you're in a crisis situation . . . and I find a little marijuana on the side does help. (male with chronic asthma).

I fell down a flight of stairs . . . and found myself in a lot of pain . . . decided to stop taking the prescribed medication because I ballooned up to 235 pounds. . . . I'm back to taking Tylenol 3s but I've reduced my intake to more than half since I've started smoking [cannabis]. (Female with chronic pain).

Only one person with HIV/AIDS reported being prescribed Marinol[®] (synthetic THC) for HIV/AIDS-related anorexia and nausea. However, he claimed that this had no noticeable effects. Apart from the perceived medical advantages of cannabis, some respondents also valued cannabis because it was relatively inexpensive or "natural":

It [Marinol[®]] is like \$700 for a month's supply of 90 pills and that's the max you can get. . . . So that's why I'd rather buy cannabis on the street with the welfare cheque (male with HIV).

Because it's a natural, organic thing, instead of taking these chemical prescriptions which I don't like. I'm a naturalist and I'd rather do something that grows naturally. (female with anorexia, bulimia and depression).

I would much rather use something natural—a plant product . . . than a chemical or pharmaceutical drug coz I found that they have a lot of side effects. (male with Crohn's disease).

Routes to Cannabis Use

The majority (n=42) of interviewees had at least some experience with cannabis as a recreational drug, and some (n=30) described a long history of recreational use (seven to 35 years). In these cases self-defined, medical cannabis use typically started when recreational use was found to be helpful for medical or psychological problems:

I had lost a lot of weight . . . I was down to like 97 pounds. When I started smoking marijuana I started just smoking it casually . . . to be part of the crowd. But, I noticed the more that I smoked, the hungrier I got and the more that I eat, I found the better I sleep. (male with HIV).

I used to smoke when I was younger but that was when I guess when I started first smoking it was more recreational, with the guys sort of thing, then I stopped for quite a long period of time—I was a very hyper person. So . . . then I decided to smoke it again. (male with insomnia).

When I used to smoke it [cannabis] for recreation I was running a lot of track and field and that's . . . when I noticed when I . . . pulled muscles and so forth the pain wasn't there at all. (male with migraine).

I had tried it for recreational use back as a teenager . . . and I found that . . . there's times when I was feeling bad with my illness and I'd smoke some and I felt better. . . . So, um, I thought that it probably might work for me and . . . It worked better than most of the medicine I was taking. (male with Crohn's disease).

I've been smoking dope for 24 years. Originally, peer pressure, getting high, now I don't even get high, I smoke it to increase my appetite . . . Can't even maintain weight unless I eat five, six times a day. Can't do that unless I smoke a couple of joints. (male with anorexia).

Respondents with no, or very limited previous experiences with cannabis (n=9) started using it medically after reading about it or on the advice of others. Two reported that they first started using cannabis on the advice of a physician:

I was drinking beer at the time . . . a friend asked me if I wanted to try it and . . . was shocked to find out how it made me feel. It was just magic. (male with AIDS).

A friend made me some Sleepy Time tea with cannabis in it. (male with Tourette's Syndrome).

Dr. . . . was seeing me for epilepsy suggested that I smoke a joint before I came for the next visit . . . and I did. . . . he was having trouble controlling the epilepsy. (male with epilepsy).

Around four or five years ago I read and even my doctor had suggested that maybe that this was a good thing . . . because of my . . . problem with wasting. (male with HIV).

Methods of Cannabis Use

Smoking was the primary and the preferred method for using cannabis either because it was inherently enjoyable or

because of its advantages over other methods of use.

I just smoke it. . . . I have tried hash brownies and I've tried marijuana brownies . . . but to me the high is not the same . . . I smoke cigarettes constantly, right? . . . to smoke a joint is the same thing as smoking a cigarette except for you're getting a buzz off a joint (male with HIV).

I've eaten it in the past. . . . I've drunk it in tea. . . . put it in sauces and cooking . . . for me immediate effective relief is smoking . . . eating is too expensive . . . smoking you don't need as much to get the effect what-have-you and it's more immediate too. (male with epilepsy).

It's just easy to do [smoking] . . . you have to put it and just light it up . . . so it's a lot easier. (male on methadone).

Some advantages to eating or drinking cannabis were identified:

In tea form . . . it effects you faster, it's absorbed faster . . . but it is a totally different high. . . . It's more of a body type stone . . . relaxes your body whereas if you smoke it, it still has the same effect but it's more of a head stone as well. (male with Crohn's Disease).

I think it's longer lasting [eating or drinking marijuana] . . . don't have to worry so much about the smell of it. (female with pain from an accident)

I worry about the respiratory side effects and the social aspects—sometimes. . . . my partner doesn't like me to smoke in the house so I step outside and the neighbors can smell it and I'm not always comfortable with that. (male with multiple HIV-related problems).

It [cannabis] can make me lazy. . . . It makes me cough. (male with depression).

What about my lungs and throat and I don't want to be smoking at all. I'm a nonsmoker at heart. (female with chronic pain).

Only two respondents said that they never smoked cannabis. One was the person with Tourette's Syndrome who reported drinking cannabis in tea. The other was a woman who used cannabis in tea or banana bread for menstrual cramps. One respondent had a novel method of using cannabis:

I'm mixing it with alcohol. . . . crushed up as a paste and rub it on my chest as a plaster for like . . . lung infections or colds. (male with migraine).

Patterns and Amount of Cannabis Use

Thirty five (70%) of respondents typically smoked cannabis every day, and among these daily users, the majority smoked two to three times a day. Those using cannabis to stimulate their appetites used it at meal times, while those who ever used cannabis to help them sleep (n=28), used it later in the evenings.

Total daily consumption was, however, quite variable. One person reported smoking up to ten joints a day while another said that she made a joint last all day by only taking a few puffs before meals. Based on reports of the costs of cannabis and typical monthly expenditures the average monthly consumption was between one and two ounces, with a range from less than one quarter ounce to over three ounces. These estimates included daily users but excluded those who reported growing their own cannabis or getting it free.

Thirteen³ respondents reported that, in most cases their use of cannabis was closely associated with symptom relief or avoidance:

I start smoking about two weeks before my period begins. (female with menstrual cramps).

If I can do without it, I do without it. Even if I have my ties back I do without it. I like to keep it for that special moment . . . when I have to make a presentation . . . [at] a board meeting. (male with Tourette's Syndrome).

However, in the majority of cases (n=37) cannabis was also used recreationally and the distinction between medical and nonmedical use was blurred:

It's beautiful when you can sit down and smoke a little joint and just get wasted out of your face . . . yes we like the high. (male with HIV).

Sometimes a friend comes over in the morning of whatever and it's like a beer on a Sunday afternoon. . . . (female with nausea).

For those few (n=13)⁴ who said they did use cannabis recreationally, the cannabis high was either seen as a medical benefit or as a state to be avoided.

I just go with it . . . it makes me feel better you know, once I start feeling better then I know I'm there . . . I just look at it as a pleasant side effect . . . getting a bit high. (male with Crohn's Disease).

The high is the one that gives me the energy. (female with HIV).

Don't like getting high because the disorganization gets worse. (male with migraine headaches).

Sources and Methods of Supply

Almost all respondents obtained cannabis from regular dealers or friends. However, two reported that they grew their own and one reported going to a buyers' club.

It seems more legitimate (going to the buyers' club) than meeting someone on the street . . . and you don't know if you're gonna get ripped off or beaten up. (male with HIV).

Only two reported that they did not have established suppliers of cannabis and went in search of cannabis whenever

they needed it:

I have to go and wait for somebody to show up at these places where they sell . . . it's too far away and sometimes I go there and they're not there. (female with HIV).

I phone people who might know somebody coz nobody I know smokes. So I'm asking them to lean on their friends. (female with chronic pain).

Finally, one respondent said that he got cannabis from his doctor:

He just gets it for me and I have to come in to get it . . . so I never get accosted by anybody. (male with HIV).

Negative Experiences Associated with Cannabis Use

About a third of those interviewed reported being stopped and searched for cannabis or other drugs and drug paraphernalia at some time. These were typically long-term recreational users, but two who saw their use of cannabis use as strictly medical had also been arrested and charged. One won a court case by convincing the judge that the cannabis was used for medical reasons, while the second was preparing to challenge a conviction for possession on the same grounds. A third, strict medical user with AIDS had been contacted by the police following a complaint from a neighbor. However, no arrest was made and the respondent felt that the police were "very humane" when they suggested that he could avoid upsetting the neighbor by smoking on a private balcony.

That cannabis is an illegal drug weighed on the minds of most respondents and they were careful to avoid being arrested. However, medical use was also seen as potentially giving immunity to serious legal consequences:

I'm HIV positive. . . . What are you going to do? Gonna send me to jail? (male with HIV).

Some respondents had been harmed by their use of cannabis, but this was not always acknowledged. One, who saw cannabis and drug use generally in a very positive light, had been severely hurt while riding a bicycle under the influence of cannabis and had since continued a dysfunctional lifestyle involving the heavy use of cannabis and other drugs. Another gave an incoherent account of how cannabis had helped him psychologically, but it appeared that some of his problems (anxiety and depression) were drug-induced. One other respondent, who suffered from depression, also speculated that this may have been made worse by cannabis use.

Having to buy on the street resulted in a financial burden for most interviewees. The appetite stimulant effects of cannabis were negative consequences for two respondents who were not using it for that reason. Most did not see cannabis as having any negative effects. However, the following negative effects were each mentioned by at least

one respondent: rejection by family members, lethargy, apathy, cough or throat irritation from smoking, thirst, loss of concentration, short-term memory loss, paranoia, severe intoxication and depression.

Many interviewees were using cannabis two or more times a day for a long time and they could be expected to experience withdrawal symptoms if they ever stopped using. However, none expressed significant concerns about cannabis dependence:

I am dependent already, it doesn't bother me. cuz I'm still ok and it helps me lead a healthy life. (female with HIV-related anorexia).

No, I'm not concerned about becoming dependent. . . . I know it's slightly habit forming but it's not a chemical addiction like cigarettes. (male with Crohn's Disease).

I do get some withdrawal effect . . . here is a little bit of concern mostly because it's illegal. . . . if I could just get it at the drugstore I wouldn't have much concern. (male with chronic pain).

I think it's more of a psychological addiction than a physical one for me because I've gone days without it. If I became dependent it would be more emotionally than physically. (male with HIV).

Experiences with Physicians

Only twelve respondents said that they had not told their physicians that they were using cannabis for medical or other reasons. Others had told their physicians and found their reactions mostly noncommittal but sometimes clearly positive. Only three said their doctors discouraged them from using cannabis:

Well he [the doctor] doesn't approve of it but in a stupid little way he does approve of it because he knows that from my . . . personal experience telling him of just how much good it's done for me. (male with HIV).

My psychiatrist is very old school. He's telling me that I can become addicted. . . . He would rather see me go through surgery and nerve blocks. (male with chronic pain).

Almost all of those with HIV/AIDS had told their physicians about their use of cannabis and had found physicians to be very understanding and supportive. Physicians were also reported as being sympathetic or supportive of cannabis use by at least one respondent suffering from nausea and weight loss associated with methadone treatment, chronic pain, epilepsy, menstrual cramps, Crohn's Disease, repetitive strain injury, and depression.

SUMMARY AND DISCUSSION

This exploratory study shows that cannabis was being used for a range of medical reasons. Among those interviewed

the most common conditions associated with cannabis use were HIV/AIDS-related problems, chronic pain, depression and anxiety. However, cannabis was also used to treat menstrual cramps, anorexia, narcotic addiction, migraine, Tourette's Syndrome, lupus, Grave's Disease, epilepsy, retinitis, chemotherapy-induced loss of appetite, Crohn's Disease, arthritis and everyday aches, pains, stresses and sleeping difficulties. Specific symptoms that were reportedly relieved by cannabis included sleeping difficulties, nausea, loss of appetite, pain, depression and anxiety, tics and seizures, loss of energy, breathing difficulties, craving for heroin, anger and vision problems. Typically, medical cannabis use followed recreational use and the majority of those interviewed were long-term, and sometimes heavy, recreational users. Most continued to use cannabis recreationally as well as medically. However, the sample also included some people whose use of cannabis was primarily initiated by the desire to treat medical conditions for which other treatments were unsatisfactory.

Almost all interviewees smoked cannabis and only two regularly used it in other forms (in tea or baked in a muffin). The majority used cannabis two to three times every day. Cannabis was usually obtained from friends or regular dealers but one person obtained it from his doctor. Respondents were acutely aware that possession of cannabis was illegal and they took precautions to avoid arrest. About a third, mostly those who used cannabis recreationally, had been stopped by police and searched for drugs. Three of those who had only used cannabis for medical reasons had been involved with the police but only two had been charged and one had won a court case. Few admitted negative experiences associated with cannabis use or expressed concerns about being dependent on it. However, some problems that seemed evident to the researchers were not always clearly acknowledged as related to cannabis (accidents, dysfunctional lifestyle, psychological problems). Most respondents had told their doctors about using cannabis for medical reasons and their doctors were supportive or noncommittal. Doctors were seen as supportive of cannabis use by most respondents with HIV/AIDS.

The present study did not, of course, seek to determine if the reported medical benefits of cannabis were real or imagined or if they should be attributed to placebo effects, other treatments or natural recovery. It is likely that the medical benefits of cannabis were sometimes overstated, especially by long-term recreational users with positive views of cannabis. Although respondents thought that their physicians supported their use of cannabis, it is not known if this was really the case. Some respondents also seemed to ignore negative consequences of cannabis use such as dependence and withdrawal.

Many reported benefits of cannabis were consistent with those reported elsewhere. Cannabis was typically used for its sedative, analgesic, antispasmodic, appetite stimulating, anticonvulsant and euphoric properties. These

properties were well known in the past century when cannabis was used to treat conditions that required medications with these properties. Although scientific evidence in favor of medical cannabis is limited (Gurley, Aranow & Katz 1998), self-treatment with cannabis could become popular as more users publicize their own experiences. This is especially so if the everyday aches and pains and psychological problems are promoted as medical reasons for using cannabis.

The boundaries of medical cannabis use will be of concern if more medical cannabis cases come to court. In the Canadian cases where medical necessity was successfully used as a defense against a charge for the possession of cannabis, the defendants had chronic and serious medical conditions (epilepsy and AIDS) and were strongly supported by their physicians. Others who are able to convince the courts that their use of cannabis brings relief to otherwise untreatable conditions may also do well in court. However, those who use cannabis for less serious conditions that can be successfully treated by other means may not fare so well, especially without a supportive physician.

The boundaries of medical use are also of concern if new policies on medical cannabis use are developed. If such use encompasses use for self-diagnosed conditions then policies might be needed to ensure that all those who want to use cannabis for these conditions have access to quality-controlled cannabis products. If on the other hand, medical use is to be defined as use with the approval of a physician, more restrictive access will be needed.

At present there are no completely satisfactory ways to deal with the issues of medical cannabis use. Apart from the difficulty of defining "medical," there are presently many uncertainties about the objective benefits of cannabis as a medicine as well as legitimate concerns about side effects and the risks associated with cannabis smoking. Many issues could eventually be resolved through scientific research, including research on alternative methods of delivery such as nasal sprays. In the meantime, there are humanitarian reasons for devising ways to ensure that the seriously ill who find cannabis helpful can have access to a quality-controlled product.

Studies of this sort always have limitations. The sample was small and drawn from one area of one city. Respondents were self-selected. The sampling strategy may have excluded those who were very sick and those who feared being identified as cannabis users. It may also have been biased towards HIV/AIDS cases as notices were put in AIDS clinics. A wider distribution of notices to psychiatric, neurological, pain and cancer treatment centres, clinics, or self-help groups may have attracted a wider range of users or a greater representation of some types. However, the study had limited resources and initially there was a concern that large numbers would come forward for interviews, but this was not the case. It took four months before

50 interviews were completed and only about 120 calls about the study were received.

It is clearly important to learn more about the extent of medical cannabis use in the general population and in populations at high risk. The present study suggests that priority should be given to studies of cannabis use among people with HIV/AIDS. Issues of concern should be the nature and extent of cannabis use as well as biomedical studies that assess the effects of cannabis on biological systems. Studies of interactions between cannabis and the drugs used in HIV/AIDS treatment should also be given priority.

NOTES

1. The notice soliciting the interview referred to marijuana and not cannabis on the assumption that most medical

users would refer to cannabis this way. The name cannabis will be used throughout this paper except when quoting respondents who referred to cannabis as marijuana.

2. All quotes use respondents own words. However, redundant words and phrases and those not directly relevant to a particular topic have been omitted. Words in brackets were added by the authors to clarify respondents statements.

3. Approximate number. Some accounts of use patterns were difficult to interpret.

4. See previous footnote.

REFERENCES

- Angus Reid Group. 1997. Canadian's view on decriminalizing marijuana smoking. Press release, November 4th.
- Beesley S. & Russell A. 1997. Cannabis use in a general psychiatric population. *Scottish Medical Journal* 42 (6):171-72.
- Blackwell, J.; Beresford, J. & Lambert, S. 1987 Cannabis self-medication and adverse reactions in psychiatric patients. *Social Pharmacology* 1: 357-68.
- Campbell, L. 1996. *Natures' Healing Herbs*. On the Internet at www.hempbc.com/backissues96/mayjune.
- Dansak, D.A. 1997. Medical use of recreational drugs by AIDS patients. *Journal of Addictive Diseases* 16 (3): 25-30.
- Gurley, R.J.; Aranow, R. & Katz, M.1998. Medical marijuana: A comprehensive review. *Journal of Psychoactive Drugs* 30 (2):137-48.
- Grinspoon, L. & Bakalar, J.B. 1997. *Marijuana, the Forbidden Medicine*. New Haven, Connecticut and London: Yale University Press.
- Harris, D.; Mendelson, J.E. & Jones, R.T. 1998. A survey of 100 medical marijuana club members (abstract). In: L.S. Harris (Ed.) *Problems of Drug Dependence. Proceedings of the 60th Annual Scientific Meeting of the College on the Problems of Drug Dependence*. NIDA Research Monograph Series No. 179. Rockville, Maryland: National Institute on Drug Abuse.
- Lindesmith Centre. 1998. American voters support drug reform. Press release, November 4th.
- Mathers, D.C.; Ghodse, A.H.; Caan, A.W. & Scott, S.A. 1991. Cannabis use in a large sample of acute psychiatric admissions. *British Journal of Addiction* 86 (6): 779-84.
- Ogborne, A.C.; Smart, R.G. & Adlaf, E.A. 2000. Self-reported medical use of marijuana: A survey of the general population. *Canadian Medical Association Journal* 162: 1685-86.
- Rohnaar, P.K.J. & Timmerman, L. 1997. Substance use in acute admissions in an urban psychiatric hospital. *Tijdschrift voor Psychiatrie* 39 (8): 649-59.
- Smart, R.G. & Ogborne, A.C. 2000. Cannabis users in the general Canadian population. *Substance Use and Misuse* 35 (3): 301-11.
- Wesner, B. 1996. *The Medical Marijuana Issue among PWAS: Reports of Therapeutic Use and Attitudes towards Legal Reform*. Working Paper Series. Manoa: Drug Research Unit, University of Hawaii.
- World Health Organization. 1997. *Cannabis: A Health Perspective and Research Agenda*. Geneva, Switzerland: World Health Organization.



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Around-the-Clock Oral THC Effects on Sleep in Male Chronic Daily Cannabis Smokers

David A. Gorelick, MD, PhD¹, Robert S. Goodwin, DO, PhD¹, Eugene Schwilke, PhD¹, Jennifer R. Schroeder, PhD², David M. Schwobe, PhD¹, Deanna L. Kelly, PharmD³, Catherine Ortemann-Renon, PharmD, PhD⁴, Denis Bonnet, MD⁴, and Marilyn A. Huestis, PhD¹

¹Chemistry and Drug Metabolism Section, National Institute on Drug Abuse, National Institutes of Health, Baltimore, Maryland ²Office of the Clinical Director, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, Baltimore, Maryland ³Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, Maryland ⁴Sanofi-Aventis Recherche, Montpellier, France

Abstract

Background and Objectives— 9-tetrahydrocannabinol (THC) promotes sleep in animals; clinical use of THC is associated with somnolence. Human laboratory studies of oral THC have not shown consistent effects on sleep. We prospectively evaluated self-reported sleep parameters during controlled oral THC administration to research volunteers.

Methods—Thirteen male chronic daily cannabis smokers (mean \pm SD age 24.6 \pm 3.7 years, self-reported smoking frequency of 5.5 \pm 5.9 (range 1–24) joint-equivalents daily at study entry) were administered oral THC doses (20 mg) around-the-clock for 7 days (40–120 mg daily) starting the afternoon after admission. The St. Mary's Hospital Sleep Questionnaire was completed every morning. Plasma THC and 11-OH-THC (active metabolite) concentrations were measured in venous blood samples collected every evening. Changes in sleep characteristics over time and associations between sleep characteristics and plasma cannabinoid concentrations were evaluated with repeated measures mixed linear regression.

Results—Higher evening THC and 11-OH-THC concentrations were significantly associated with shorter sleep latency, less difficulty falling asleep, and more daytime sleep the following day. In contrast, the duration of calculated and self-reported nighttime sleep decreased slightly (3.54 and 5.34 minutes per night, respectively) but significantly during the study.

Conclusions—These findings suggest that tolerance to the somnolent effects of THC may have occurred, but results should be considered preliminary due to design limitations.

Address correspondence to Dr. Huestis, Chemistry and Drug Metabolism Section, IRP, National Institute on Drug Abuse, National Institutes of Health, 251 Bayview Blvd., Room 05A721, Baltimore, MD 21224. mhuestis@intra.nida.nih.gov.

Declaration of Interest

Authors Bonnet and Ortemann-Renon are employees of Sanofi-Aventis. The other authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

Scientific Significance—Somnolence from oral THC may dissipate with chronic, high-dose use. This has implications for patients who may take chronic oral THC for medicinal purposes, including cannabis dependence treatment.

INTRODUCTION

Cannabis, the most widely used illegal drug,¹ generally promotes sleep by activating cannabinoid CB1 receptors.^{2,3} This also is true of its primary psychoactive constituent, 9-tetrahydrocannabinol (THC), whose oral formulation is approved for medical use in many countries. The approved product labeling for synthetic THC (dronabinol, Marinol® Untimed Pharmaceuticals, Marietta, GA) includes somnolence as a common side effect, reported in up to 10% of patients in clinical trials. However, human laboratory studies involving controlled administration of oral THC have not shown consistent effects on nighttime sleep latency or duration with single 1.5–30 mg doses,^{4,5} 20–40 mg daily for up to 14 days,^{4,6,7} or 210 mg daily for 16 days.⁸ Interpretation is limited by small sample sizes (2–10 subjects per study) and heterogeneity in degree of cannabis use at the time of study.³ We are not aware of any prior study that evaluated the relationship between sleep characteristics and plasma cannabinoid concentrations.

As part of a larger study on human cannabis withdrawal⁹ (registered as NCT01041170 at www.clinicaltrials.gov), we had the opportunity to evaluate effects on nighttime sleep of around-the-clock oral THC (increasing from 40 to 120 mg daily) for 7 days in 13 male chronic daily cannabis smokers. Furthermore, we examined the correlation of sleep effects with evening plasma cannabinoid concentrations.

METHODS

Participants

The study was approved by the institutional review boards of the National Institute on Drug Abuse (NIDA) Intramural Research Program, the University of Maryland School of Medicine, and the Maryland Department of Health and Mental Hygiene. All participants provided written informed consent when not acutely intoxicated or in withdrawal. Inclusion criteria were 18–45 years old, smoked cannabis for the prior 1 year and averaging daily use for at least 3 months prior to admission, cannabis use within 24 hours of admission, urine specimen positive for cannabinoids in the 30 days prior to study entry, normal cardiac function, and IQ ≥ 85 (based on the Wechsler Abbreviated Scale of Intelligence). Exclusion criteria consisted of past or present clinically significant medical disease that might interfere with safe study participation; history of psychosis or any current DSM-IV axis I disorder (other than cannabis, caffeine, or nicotine dependence, or simple phobia); current physical dependence on substances other than cannabis, nicotine, or caffeine; history of clinically significant adverse events associated with cannabis intoxication or withdrawal, for example, psychosis; ≥ 6 alcohol drinks/day ≥ 4 times/week in the month prior to study entry; sesame oil allergy; or current interest or participation in drug abuse treatment.

Participants were admitted to a secure research unit the evening before Day 1, 17.5–21 hours before their first oral THC dose. The unit had 24-hour staffing, ensuring that subjects had no

access to drugs except those provided in the study. Fourteen participants enrolled in the study; 13 completed.

Oral THC Administration

An escalating dose design was utilized. Oral synthetic THC (dronabinol, Marinol®) was administered in 20 mg capsules with increasing frequency (every 4–8 hours) for total daily doses as follows: 40 mg on Day 1; 100 mg on Days 2–4; and 120 mg on Days 5 and 6. All dosing occurred between 06:00 and 24:00, except for a 02:00 dose on Day 3. The first dose was administered on Day 1 at 15:00, 17.5–21 hours after admission to the research unit. This regimen standardized cannabis tolerance across participants while minimizing adverse events previously reported with 30 mg THC doses.¹⁰

Assessments

Sleep—Participants' sleep characteristics prior to admission to the research unit were assessed with the Johns Hopkins Sleep Center Sleep History Questionnaire (SHQ) (92 six- or seven-point Likert scale items)¹¹ and the Boredom–Eveningness Questionnaire (MEQ) (6 clock time items and 13 four-point Likert scale items)¹² completed within one week of admission. This data provided baseline sleep characteristics prior to THC dosing.

After admission, subjects completed every morning (08:00–10:15) the St. Mary's Hospital Sleep Questionnaire,¹³ a 14-item instrument assessing duration and quality of the previous night's sleep. This questionnaire has previously been employed in outpatient¹⁴ studies of cannabis smokers.

In addition, the subjective feeling of “sedated” was assessed with a 100 mm Visual Analogue Scale (VAS) every night at 20:00 (as part of a larger battery of 11 VAS evaluating symptoms of cannabis intoxication and withdrawal).⁹ The VAS was anchored at the left with “not at all” and at the right with “most ever.” The VAS score was the number of mm the participant marked to the right of the left anchor point.

Pharmacokinetics—Peripheral blood was collected periodically through an indwelling venous catheter for quantification of THC and its pharmacologically active metabolite 11-hydroxy-THC (11-OH-THC). Specimens were collected in heparinized tubes, stored on ice no more than 2 hours prior to centrifugation, and separated plasma stored refrigerated at 4°C until analysis by two-dimensional gas chromatography mass spectrometry with cryofocusing (2D-GCMS),¹⁵ with a limit of quantification of 0.25 ng/ml for THC and 0.5 ng/ml for 11-OH-THC. Specimens were collected the evening of admission and thrice daily (08:00 or 10:00, 20:00 or 20:30, and 22:00 or 22:30) on Days 1–8. Plasma cannabinoid concentrations in six of these participants were previously reported.¹⁶

Statistical Methods

Comparisons between variables employed *t* tests. Associations between pairs of variables were evaluated with Pearson correlation coefficients. Changes in sleep characteristics over time and the associations between sleep and participant characteristics were evaluated with repeated measures mixed linear regression, which allowed inclusion of data from the three

non-completers. Participant baseline characteristics of age, years of regular cannabis use, and joints smoked per day were used as static covariates; study day, feeling sedated the night before, and plasma cannabinoid concentrations as time-varying covariates. Separate regression models were fit for each sleep variable, using an unstructured covariance structure and random intercept. Regression coefficients are reported as mean \pm SE. A p -value <0.05 was considered statistically significant. All analyses were conducted with SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Participants

Fourteen participants enrolled in the larger study⁹: one was discharged prior to receiving any medication because the study was terminated, one withdrew after 1 day of oral THC dosing for personal reasons, two were discharged on the fourth day of dosing (one due to premature ventricular contractions and one due to psychological reactions to THC), and 10 completed 8 days of dosing. All 13 participants (13 male, 10 African American, 2 Caucasian, 1 mixed race, mean \pm SD age 24.6 ± 3.7 years) who received THC are included in this analysis. These participants first smoked cannabis at 14.0 ± 2.4 years of age and began regular (at least weekly) smoking at age 15.6 ± 3.7 years. All but one participant reported at least 1,000 lifetime cannabis uses; eight reported at least 5,000 uses. All participants smoked cannabis joints and/or blunts (cannabis wrapped in tobacco leaves); five also had smoked hashish in the past. Seven participants reported lifetime experience with cannabis tolerance (needing to smoke more to get the same effect); five of these seven also reported experiencing cannabis withdrawal. At the time of study entry, participants averaged 5.5 ± 5.9 (median = 3, range 1–24) joints daily. All participants self-reported cannabis smoking in the 24 hours prior to admission; all had a positive cannabinoid urine test upon admission.

All 13 participants were lifetime cigarette smokers; 9 were daily smokers at the time of study entry, averaging 17.9 ± 18.8 (median = 10, range 2–50) cigarettes daily. The remaining 4 participants abstained from tobacco smoking for 4 and 6 months, and 8 and 10 years prior to admission. All participants were lifetime alcohol drinkers, although two abstained for 1 month prior to study entry. The 11 current drinkers averaged 12.1 ± 10.9 (median = 12, range 0.25–32) standard drinks per week over the 3 months prior to study screening. Two participants reported current oral amphetamines intake, averaging two pills each week. There was no other current illicit drug use.

Pre-admission Sleep Characteristics

Ten participants reported no sleep problems prior to admission. Three reported one sleep problem each: one prolonged sleep latency (1 hour), one disturbed sleep (“tossing and turning”), and one early morning awakening. The majority of participants (10 of 13) reported good to very good sleep quality on the SQI. Four participants reported “almost always” smoking cannabis to help sleep; eight others reported “sometimes” smoking cannabis for this purpose. In contrast, only four participants “rarely” ingested alcohol to help sleep and two “rarely” took sleeping pills. No participant reported ever taking other

medication to help sleep. Quantitative pre-admission sleep characteristics are listed in Table 1.

Internal Validity of St. Mary's Hospital Sleep Questionnaire Data

In-bed time was earlier than fall-asleep time for all participants on all days. Get-out-of-bed time was later than wake-up time on all except two questionnaires. Calculated hours of nighttime sleep (time woke up \pm time fell asleep) did not differ significantly from self-reported duration of sleep: mean difference $.03 \pm .6$ hours ($t = .5$, $p = .61$), median and modal values both zero. Similarly, calculated sleep latency (time fell asleep – time got into bed) did not differ significantly from self-reported how long to fall asleep: mean difference $.063 \pm .33$ hours ($t = 1.9$, $p = .06$), median and modal values both zero.

Conceptually related sleep variables were significantly associated in the expected directions. Difficulty falling asleep was positively associated with sleep latency, that is, participants reporting greater difficulty falling asleep also reported longer duration of time to fall asleep ($.52 \pm .13$, $p = .0002$). Duration of nighttime sleep was positively associated with both depth of sleep ($.22 \pm .085$, $p = .012$) and quality of sleep ($.39 \pm .090$, $p < .0001$). Number of nighttime awakenings was negatively associated with both depth of sleep ($-.49 \pm .12$, $p < .0001$) and quality of sleep ($-.71 \pm .12$, $p < .0001$).

First Night Sleep Characteristics

Participants spent a mean (\pm SD) of 7.1 ± 1.3 hours in bed and 5.9 ± 1.3 hours asleep their first night on the research unit, prior to receiving any oral THC. Their sleep latency was 1.0 ± 0.7 hours and they reported 1.6 ± 1.9 nighttime awakenings. Almost one-third (30.8%) reported little or no difficulty falling asleep (23.1% reported a lot or extreme difficulty), less than one-quarter (23.1%) reported less than average depth of sleep, 84.6% reported good sleep quality, and a majority (61.6%) reported being completely alert (less than a third [30.8%] reported any drowsiness) the next morning (ie, morning of Day 1).

First night sleep characteristics (assessed by the St. Mary's Hospital Sleep Questionnaire) were not generally similar to participant's self-reported typical pre-admission sleep characteristics (assessed by the SQI). Correlations between first night and typical pre-admission hours in bed, sleep duration, sleep quality, and next morning alertness were generally low and not significant ($-.17$, $p = .57$; $.27$, $p = .37$; $-.17$, $p = .59$; and $-.52$, $p = .07$, respectively). In particular, hours in bed and sleep duration were shorter on Day 1 than pre-admission, while ratings of sleep quality were higher (Table 1).

Changes in Sleep Characteristics with Oral THC Dosing

The first THC doses, administered the afternoon of Day 1 (20 mg each at 15:00 and 20:00), after at least 17.5 hours of abstinence, had no acute effect on sleep parameters compared to the first night on the research unit, before THC administration (ie, comparing Day 2 vs. Day 1 values, Table 1). There were small but statistically significant decreases in both calculated hours asleep (mean 3.54 fewer minutes per night; $-.059 \pm .026$, $p = .025$) and self-reported hours of nighttime sleep (mean 5.34 fewer minutes per night; $-.089 \pm .031$, $p = .005$) over

the 7 nights of the study. None of the other eight sleep variables showed any significant change over the 7 days of oral THC dosing (Table 1).

Association of Sleep Characteristics with Plasma Cannabinoid Concentrations and Subject Baseline Characteristics

Higher evening plasma concentrations of THC, its active metabolite 11-OH-THC, and THC + 11-OH-THC, were significantly associated with shorter sleep latency ($-.0091 \pm .0045$, $p = .046$; $-.022 \pm .0091$, $p = .015$; and $-.0069 \pm .0031$, $p = .028$, respectively) and lower self-rated difficulty falling asleep ($-.015 \pm .0064$, $p = .023$; $-.028 \pm .013$, $p = .035$; and $-.010 \pm .0044$, $p = .023$, respectively). Evening plasma concentrations of THC and THC + 11-OH-THC also predicted more hours of daytime sleep the following day ($.019 \pm .0075$, $p = .011$; and $.013 \pm .0052$, $p = .017$, respectively). There were no other significant bivariate associations.

Duration of regular cannabis smoking was positively associated with hours spent in bed and morning alertness upon waking. For every additional year that a participant had used cannabis regularly, they spent .08 hours longer in bed ($.081 \pm .040$, $p = .046$) and reported .35 units greater morning alertness ($.35 \pm .17$, $p = .043$). African American participants were associated with fewer hours of daytime sleep ($-1.55 \pm .24$, $p < .0001$). Intensity of self-reported sedation in the evening was positively associated with number of awakenings that night ($.029 \pm .012$, $p = .014$).

DISCUSSION

This study showed the feasibility of assessing sleep characteristics in adult chronic daily cannabis smokers exposed to around-the-clock dosing with oral THC for 7 days on a secure residential research unit. The study found no acute effect of THC on sleep characteristics the second night on the research unit (after at least 17.5 hours of abstinence). This finding is consistent with previous single-dose human laboratory studies with 1.5–30 mg THC,^{4,5,17} but not with animal studies² or clinical reports of somnolence associated with oral THC (dronabinol) use. It is possible that any sleep-promoting effect of the initial oral THC doses (40 mg) was counteracted, and thereby masked, in our study (and in prior human laboratory studies) by the sleep disturbance engendered by admission to an unfamiliar environment (the research unit).¹⁸ Such a novelty-induced transient insomnia would also explain the dissimilarity between participants' self-reported typical pre-admission sleep characteristics and their sleep characteristics on the first night on the research unit. This issue could be addressed in future studies by administering THC only after subjects had spent sufficient time in the research environment to ensure complete adaptation.

Around-the-clock THC dosing was associated with a small (about 5 minutes per night) but statistically significant decrease in overall hours of nighttime sleep during the 7 dosing days. This suggests the possible development of tolerance to any somnolent effect of THC. However, higher evening plasma concentrations of both THC and its active metabolite 11-OH-THC were associated with shorter sleep latency and less self-rated difficulty falling asleep that night, and THC alone and in combination with 11-OH-THC was associated with more hours of daytime sleep the following day, suggesting that cannabinoids maintained

some of their sleep-promoting properties throughout the study. This is consistent with participants' reported pre-admission intake of cannabis as a sleep aid. The mechanisms contributing to the balance between the acute somnolent effect of cannabinoids and development of tolerance to this effect with around-the-clock dosing for 7 days remain unclear. A modest worsening of sleep characteristics with chronic oral THC dosing may not have been detected in prior human laboratory studies because of small sample sizes. We are aware of three such studies administering oral THC for at least 6 days: one had two subjects,⁶ one three,⁴ and one seven subjects.⁸

The findings of this study should be considered preliminary because of design limitations. First, all data was collected by participant self-report, rather than staff observation or polysomnography. However, the major data collection instrument employed, the St. Mary's Hospital Sleep Questionnaire, is widely utilized in clinical research,¹⁹ and has been used in studies of cannabis smokers.¹⁴ Furthermore, the high degree of consistency on several internal validity checks suggests that participants were providing valid data. Even if there were some inaccuracies in the sleep data, one would have to assume a varying bias over time to completely invalidate the within-subject findings of this study. Second, there was no THC placebo group. Thus, it remains possible that stronger than observed somnolent effects of higher evening plasma cannabinoid concentrations were masked by other non-pharmacological factors in the research setting. Third, THC dosing began while participants were likely in early acute cannabis withdrawal and data collection began the first night on the research unit. Thus, the observed findings could have been influenced by both cannabis withdrawal and acclimation to sleeping in a new environment.

CONCLUSIONS

This study, with a sample size almost double that of previously published human laboratory studies, observed only modest sleep-enhancing effects of around-the-clock dosing with oral THC (40–120 mg daily) for 7 days in 13 male daily cannabis smokers. The effects of such THC dosing on sleep were limited to shorter sleep latency and less difficulty falling asleep associated with higher evening plasma cannabinoid concentrations. The overall amount of nighttime sleep decreased slightly during the study, suggesting that tolerance to the somnolent effects of THC may have occurred. These findings are largely inconsistent with reports of somnolent side-effects with clinical oral THC therapy, but should be considered preliminary because of design limitations. Larger studies with objective sleep measures (eg, polysomnography) in subjects acclimated to the research environment before exposure to THC are warranted.

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REFERENCES

1. United Nations Office on Drug and Crime. UN World Drug Report 2010. Vienna: 2011.
2. Murillo-Rodríguez E. The role of the CB1 receptor in the regulation of sleep. *Progr Neuro-Psychopharmacol Biol Psychiatry*. 2008; 32:1420–1427.
3. Schierenbeck T, Riemann D, Berger M, et al. Effect of illicit recreational drugs upon sleep: Cocaine, ecstasy and marijuana. *Sleep Med Rev*. 2008; 12:381–389. [PubMed: 18313952]
4. Freemon FR. The effect of delta-9 tetrahydrocannabinol on sleep. *Psychopharmacologia*. 1974; 35:39–44.
5. Hosko MJ, Kochar MS, Wang RIH. Effects of orally administered delta-9-tetrahydrocannabinol in man. *Clin Pharm Therap*. 1973; 14:344–352.
6. Freemon F. The effect of chronically administered delta-9-tetrahydrocannabinol upon the polygraphically monitored sleep of normal volunteers. *Drug Alcohol Depend*. 1982; 10:345–353. [PubMed: 6299682]
7. Haney M, Gunderson EW, Rabkin J, et al. Dronabinol and marijuana in HIV-positive marijuana smokers: Caloric intake, mood, and sleep. *J Acquir Immune Defic Syndr*. 2007; 45:545–554. 510.1097/QAI.1090b1013e31811ed31205. [PubMed: 17589370]
8. Feinberg I, Jones R, Walker JM, et al. Effects of high dosage delta-9-tetrahydrocannabinol on sleep patterns in man. *Clin Pharmacol Therap*. 1975; 17:458–466. [PubMed: 164314]
9. Gorelick DA, Goodwin RS, Schwilke E, et al. Antagonist-elicited cannabis withdrawal in humans. *J Clin Psychopharmacol*. 2011; 31:603–612. [PubMed: 21869692]
10. Haney M, Ward AS, Comer SD, et al. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology*. 1999; 141:385–394. [PubMed: 10090646]
11. Bolla KI, Lesage SR, Gamaldo CE, et al. Sleep disturbance in heavy marijuana users. *Sleep*. 2008; 31:901–908. [PubMed: 18548836]
12. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol*. 1976; 4:97–110. [PubMed: 1027738]
13. Ellis BW, Johns MW, Lancaster R, et al. The St. Mary's Hospital Sleep Questionnaire: A study of reliability. *Sleep*. 1981; 4:93–97. [PubMed: 7232974]
14. Carpenter KM, McDowell D, Brooks DJ, et al. A preliminary trial: Double-blind comparison of nefazodone, bupropion-SR, and placebo in the treatment of cannabis dependence. *Am J Addic*. 2009; 18:53–64.
15. Lowe RH, Karschner EL, Schwilke EW, et al. Simultaneous quantification of delta-9-tetrahydrocannabinol (THC), 11-hydroxy-delta-9-tetrahydrocannabinol (11-OH-THC), and 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THCCOOH) in human plasma using two-dimensional gas chromatography, cryofocusing, and electron impact-mass spectrometry. *J Chromatogr A*. 2007; 1163:318–327. [PubMed: 17640656]
16. Schwilke EW, Schwoppe DM, Karschner EL, et al. Delta-9-tetrahydrocannabinol (THC), 11-hydroxy-THC, and 11-Nor-9-carboxy-THC plasma pharmacokinetics during and after continuous high-dose oral THC. *Clin Chem*. 2009; 55:2180–2189. [PubMed: 19833841]
17. Nicholson AN, Turner C, Stone BM, et al. Effect of delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. *J Clin Psychopharmacol*. 2004; 24:305–313. [PubMed: 15118485]
18. Agnew H, Webb W, Williams R. The first night effect: An EEG study of sleep. *Psychophysiology*. 1966; 2:263–266. [PubMed: 5903579]
19. Moul DE, Hall M, Pilkonis PA, et al. Self-report measures of insomnia in adults: Rationales, choices, and needs. *Sleep Med Rev*. 2004; 8:177–198. [PubMed: 15144961]

TABLE 1
Sleep characteristics of 13 male chronic daily cannabis smokers taking around-the-clock oral THC

	Pre-admission	Day 1 (N = 13)	Day 2 (N = 13)	Day 3 (N = 12)	Day 4 (N = 12)	Day 5 (N = 12)	Day 6 (N = 10)	Day 7 (N = 10)	Day 8 (N = 10)
Duration in bed (hour)	8.5 ± 1.6	7.1 ± 1.3	6.8 ± 0.8	7.0 ± 0.4	6.6 ± 0.8	6.9 ± 0.6	6.6 ± 0.8	6.8 ± 0.7	6.8 ± 0.7
Sleep latency (hour)		1.0 ± 0.7	0.8 ± 0.8	0.4 ± 0.3	0.6 ± 0.3	0.6 ± 0.4	0.8 ± 0.7	0.7 ± 0.3	1.0 ± 0.9
Difficulty falling asleep		2.1 ± 1.0	1.5 ± 0.5	1.2 ± 0.4	2.0 ± 1.7	1.8 ± 1.1	1.4 ± 0.5	1.5 ± 0.7	2.1 ± 1.5
Duration of nighttime sleep (hour)	6.8 ± 1.7	6.2 ± 1.0	5.8 ± 1.5	6.3 ± 0.7	6.2 ± 0.7	6.1 ± 0.6	5.8 ± 0.3	5.9 ± 0.9	5.7 ± 0.7
Duration of daytime sleep (hour)		0.5 ± 1.2	0.2 ± 0.6	1.3 ± 1.7	1.1 ± 1.4	0.8 ± 1.6	0.7 ± 1.2	0.5 ± 0.6	0.7 ± 0.9
Depth of sleep		3.9 ± 1.3	3.5 ± 1.1	4.5 ± 0.9	4.3 ± 0.9	4.6 ± 0.9	4.2 ± 1.2	4.7 ± 0.8	4.5 ± 0.8
Quality of sleep	2.5 ± 1.2	4.3 ± 1.3	3.9 ± 1.1	4.5 ± 0.5	4.3 ± 0.8	4.2 ± 0.8	4.2 ± 0.8	4.2 ± 1.1	4.3 ± 0.5
Nighttime awakenings (#)		1.6 ± 1.9	2.0 ± 2.0	1.2 ± 0.6	1.4 ± 1.6	1.2 ± 0.7	1.4 ± 1.3	1.6 ± 1.3	1.3 ± 1.4
Post-awakening duration in bed (AM)		0.2 ± 0.5	0.1 ± 0.2	0.1 ± 0.1	0.03 ± 0.3	0.2 ± 0.3	0.2 ± 0.1	0.3 ± 0.2	0.2 ± 0.2
Alertness (AM)	2.9 ± 0.5	3.1 ± 1.8	7.1 ± 10.2	3.2 ± 1.5	5.7 ± 5.7	2.9 ± 1.8	3.7 ± 0.9	3.5 ± 1.8	8.9 ± 16.2

Participants were admitted to the closed research unit the evening of Day 0 and received around-the-clock oral THC dosing starting 15:00 on Day 1. The St. Mary's Hospital Sleep Questionnaire was administered each morning. Pre-admission sleep characteristics are based on the Sleep Quality Index and Morningness–Eveningness Questionnaire completed within one week of admission. Data are presented as mean ± standard deviation.

Medical cannabis – the Canadian perspective

Gordon D Ko^{1,2}

Sara L Bober¹

Sean Mindra³

Jason M Moreau¹

¹Apollo Applied Research Inc.,

²Department of Medicine, Sunnybrook

Health Sciences Centre, University

of Toronto, Toronto, ³University of

Ottawa Medical School, Ottawa,

ON, Canada

Abstract: Cannabis has been widely used as a medicinal agent in Eastern medicine with earliest evidence in ancient Chinese practice dating back to 2700 BC. Over time, the use of medical cannabis has been increasingly adopted by Western medicine and is thus a rapidly emerging field that all pain physicians need to be aware of. Several randomized controlled trials have shown a significant and dose-dependent relationship between neuropathic pain relief and tetrahydrocannabinol – the principal psychoactive component of cannabis. Despite this, barriers exist to use from both the patient perspective (cost, addiction, social stigma, lack of understanding regarding safe administration) and the physician perspective (credibility, criminality, clinical evidence, patient addiction, and policy from the governing medical colleges). This review addresses these barriers and draws attention to key concerns in the Canadian medical system, providing updated treatment approaches to help clinicians work with their patients in achieving adequate pain control, reduced narcotic medication use, and enhanced quality of life. This review also includes case studies demonstrating the use of medical marijuana by patients with neuropathic low-back pain, neuropathic pain in fibromyalgia, and neuropathic pain in multiple sclerosis. While significant preclinical data have demonstrated the potential therapeutic benefits of cannabis for treating pain in osteoarthritis, rheumatoid arthritis, fibromyalgia, and cancer, further studies are needed with randomized controlled trials and larger study populations to identify the specific strains and concentrations that will work best with selected cohorts.

Keywords: randomized controlled trials, tetrahydrocannabinol, addiction, social stigma, fibromyalgia, neuropathic pain

Medical cannabis in history and society

Cannabis sativa (cannabis) has been used therapeutically for almost 5,000 years, beginning in traditional Eastern medicine.¹ Some of the earliest evidence for this is found in the *pen-ts'ao ching*, the world's first pharmacopeia, compiled based on ancient Chinese practices from as early as 2700 BC.¹ It was not until 1841 that medical cannabis was introduced into Western medicine through the work of William O'Shaughnessy, an Irish physician, who encountered “Indian hemp” in Calcutta. By the late 19th century, medical cannabis became widely disseminated in the Americas; cannabis-based extracts, tinctures, cigarettes, and plasters produced by early prominent drug companies^{2,3} were indicated for a wide range of conditions, many of which were related to pain.^{1,4} Even Sir William Osler, the preeminent Canadian internist, wrote in *The Principles and Practice of Medicine* (1892) that “Cannabis Indica is probably the most satisfactory remedy for migraines”. However, the medical use of

Correspondence: Gordon D Ko
Apollo Applied Research Inc., 201-240
Duncan Mill Road, Toronto, ON M3B
3S6, Canada
Email jean@drkoprp.com



cannabis fell from favor in the 1930s and 1940s when fear escalated that recreational use of cannabis may be related to violence, crime, and other socially deviant behaviors. At that time, widespread prohibitive legislation banning the use of cannabis-based medicines occurred across the world.² More recently, the medical use of cannabis has been reintroduced in a number of countries for the treatment of a variety of conditions, including pain.^{5,6}

Indeed, support for medical cannabis appears to be on the rise. Overwhelmingly, patients prescribed medical cannabis for pain-related illnesses report being highly successful with pain reduction as well as with reducing their use of other medications. In a recent large survey of medical cannabis users in Arizona, 77% of fibromyalgia patients, 63% of patients with arthritis, and 51% of patients suffering from neuropathic pain reported experiencing “a lot or almost complete overall pain relief”.⁷ Most patients with these conditions (94% of patients with fibromyalgia, 81% of arthritic patients, and 61% of patients with neuropathy) also found that they were able to lower their use of their other medications such as narcotic opioids.⁷ In fact, 75% of opioid-dependent medical cannabis users reported experiencing “a lot or almost complete overall relief” from opioid dependency.⁷ Studies such as this shed light onto the wide range of clinical uses of medical cannabis, making it highly useful, since evidence from controlled clinical trials is still emerging.

Studies examining the characteristics of medical cannabis patients in the US have revealed that the majority medicate daily⁷⁻⁹ and consume 6–9 g of cannabis per week.⁸ In Canada, 42% of medical cannabis patients reported medicating two to three times per day, and 40% consume >14 g per week.¹⁰ In both Canada and the US, most patients choose inhalation as their preferred method of consumption.^{7,10}

In addition to patients with access to prescribed medical cannabis, there is also a huge population of users who consume cannabis recreationally or for self-defined medical reasons. Cannabis is the most commonly used illicit drug in the world,¹¹ with 7% of adults in the US reporting use within the last 30 days and 34% reporting having used in 2015.¹² Interestingly, only 53% of adult cannabis users in the US consume cannabis exclusively for recreational purposes, while the other 47% of users consume cannabis “in part or entirely for medicinal purposes”, with 10% using solely for medicinal purposes.¹² In Canada, ~4% of residents over the age of 14 reported at least one instance of past-year cannabis use to treat self-defined medical conditions in 2004.^{13,14}

Cannabis and pain: mechanistic considerations

The cannabis plant contains many biologically active chemicals, including ~60 cannabinoids.¹⁵ The cannabinoids are a group of molecules that bind to cannabinoid receptors and include three varieties: phytocannabinoids, which are derived from cannabis plants; synthetic cannabinoids (such as nabilone [Cesamet] – a synthetic analog of Δ^9 -tetrahydrocannabinol [THC] with a high bioavailability [$\geq 60\%$]¹⁶⁻¹⁹); and endogenous cannabinoid receptor ligands or endocannabinoids. THC is the primary psychoactive component found within cannabis, and has been shown to have analgesic effects.²⁰ However, increasing evidence has highlighted numerous roles for other phytocannabinoids, particularly cannabidiol (CBD), a non-psychoactive component with anti-inflammatory,²¹ analgesic,^{22,23} and antipsychotic^{24,25} properties. THC and CBD (Figure 1) are biosynthesized as delta-9-tetrahydrocannabinolic acid and cannabidiolic acid, respectively, from a common precursor,²⁶ and require decarboxylation by heat or extraction to produce THC and CBD properties.²⁷ Other phytocannabinoids with potential therapeutic applications include cannabigerol, cannabichromene, cannabinol, cannabidivarin, and tetrahydrocannabivarin.²⁸

THC mimics the action of the endogenous cannabinoid receptor ligands anandamide and 2-arachidonylglycerol.²⁹ Both THC and anandamide are partial agonists of CB1 receptors,^{27,29} which are primarily expressed in the central nervous system, especially in areas associated with pain, including the spinal trigeminal nucleus, amygdala, basal ganglia,³⁰ and the periaqueductal gray.^{31,32} At the cellular level, centrally expressed CB1 receptors are localized on the terminals of presynaptic neurons.³³ The endocannabinoids that bind these receptors act as retrograde signaling molecules; that is, they are synthesized postsynaptically and travel backward across the synapse to inhibit presynaptic neurotransmission.³⁴ It is believed that, within regions associated with nociception, THC induces analgesia by binding presynaptic CB1 receptors, inhibiting neurons activated by pain in these areas.

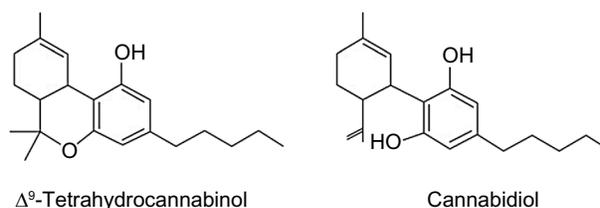


Figure 1 Diagram showing the chemical structure of Δ^9 -tetrahydrocannabinol and cannabidiol.

CBD has intrinsic analgesic and anti-inflammatory properties of its own^{22,23,35} and antagonizes several adverse effects of THC, including sedation,^{27,36} tachycardia,^{27,37} and anxiety.³⁸ CBD also ameliorates the psychoactive effects of THC,³⁸ a concern for many medical cannabis patients. Unlike THC, CBD has low affinity for CB1 receptors³⁹ and exerts analgesic actions by binding multiple proteins related to pain. For example, CBD has been shown to bind TRPV1 and mediate its desensitization³⁹ and to inhibit inactivation of anandamide,³⁹ both of which contribute to its analgesic actions. CBD also has potent anti-inflammatory properties,²¹ and may reduce pain by indirectly limiting inflammation at the site of injury.

Cannabis and pain: clinical evidence

Although significant preclinical data have highlighted the potential therapeutic benefits of smoked cannabis for pain relief in patients suffering from osteoarthritis, rheumatoid arthritis, fibromyalgia, and cancer, no randomized controlled trials (RCTs) have been carried out for these conditions.⁴⁰ However, several RCTs have evaluated the analgesic efficacy of cannabis for patients with neuropathic pain.^{41–46} In a recent meta-analysis, the individual participant data from five of these studies were synthesized to determine the overall effect of inhaled cannabis on chronic neuropathic pain.⁴⁷ All studies included in the meta-analysis compared the analgesic efficacy of cannabis with THC content ranging from 3.5% to 9.4% against that of placebo, and had periods of follow-up ranging from days to weeks.

The proportion of patients who participated in the five RCTs with a >30% improvement in chronic pain score following cannabis therapy was determined, and these patients were classified as “responders”, effectively creating a useful dichotomy for comparing response data between interventions. The meta-analysis concluded that inhaled cannabis results in a number needed to treat value to reduce chronic pain by >30% of 5.6. This needed to treat value rivals that of currently available therapeutics for chronic neuropathic pain,⁴⁸ which is typically well above 8.^{47,49–51} The authors also found that the analgesia provided by cannabis was dose-dependent, with higher THC content producing more pronounced pain relief. This finding provides additional support for the notion that cannabis is an effective analgesic for chronic neuropathic pain.

Cannabis and cancer

Medical cannabis is also used for some cancer patients to relieve symptoms including nausea and vomiting (often caused by some cancer treatments such as chemotherapy

and radiation therapy), loss of appetite, and pain. However, more research is required to identify strains and dose of medical cannabis that provide the optimal symptom relief with minimal side effects for this population.⁵²

Pharmacokinetics

To date, most pharmacokinetic studies of cannabinoids have focused on the bioavailability of inhaled THC, which varies substantially in the literature, likely due to differences in factors such as breath-hold length, source of cannabis material, and method of inhalation.^{53,54} In general, 25%–27% of the available THC becomes available for the systemic circulation after smoking.^{55,56}

The latency of effect onset for inhaled cannabis is shorter than that for cannabis consumed orally, requiring only minutes from the time of consumption to see observable changes, compared to hours when taken by the oral route.^{57–59} Furthermore, cannabis taken orally results in lower peak THC levels in the blood, but effects are observed for a longer period of time.⁵³

Hepatic cytochrome p450 enzymes govern cannabinoid bioavailability. THC is metabolized primarily by CYP 2C9, 2C19, and 3A4,⁵³ and drugs that inhibit these enzymes, including proton pump inhibitors, HIV protease inhibitors, macrolides, anti-mycotics, calcium antagonists, and some antidepressants, can increase the bioavailability of THC.^{60–62} Conversely, drugs that potentiate hepatic enzymes responsible for metabolism of THC will lower its bioavailability. Examples include phenobarbital, phenytoin, troglitazone, and St John’s wort.^{60,62}

Common concerns regarding cannabis

Patients

When it comes to patient concerns, an acronym to remember is HASH.

“High” feeling

Contrary to common misconceptions about patients seeking access to medical cannabis, many patients prefer to avoid “feeling high”. This can be mitigated fairly easily through prescribing practice, since the psychoactive effects of cannabis are primarily associated with high-THC strains. Strains of cannabis containing high levels of CBD generally make patients feel less high, since CBD acts as an antagonist to the psychoactive effect of THC.³⁸ A number of high-CBD, low-THC strains are available for patients concerned about feelings of highness and euphoria.

Acquisition cost

Medical cannabis is not typically covered by insurance plans in Canada. This can cause a significant concern for chronic pain patients who are often disabled, retired, or unable to work.⁶³ Fortunately, special pricing is available through some licensed producers for individuals receiving federal and provincial financial assistance. Examples of financial assistance for medical cannabis pricing include the Canadian Pension Plan-Disability, the War Veterans allowance, and the Ontario Disability Support Program. The price of medical cannabis is not currently regulated in Canada. The price is set by the Health Canada-authorized licensed producers and generally ranges from \$5 to \$15 per gram.⁶⁴ Generally, higher THC content is associated with a higher price per gram.

Social stigma

Many chronic pain patients considering medical cannabis anticipate disapproval from their friends and family. It is not uncommon for patients to avoid disclosing their medical cannabis use to their loved ones altogether, despite experiencing significant improvements in their pain management and quality of life. These concerns are rooted in societal stigmatization of cannabis and can often be mitigated by enabling patients to medicalize their approach to disclosure. By explaining to friends and family that cannabis has been prescribed to them as a medicine which is used to treat a variety of conditions, patients may avoid some of the stigmatization associated with use of medical cannabis. Empowering patients with evidence-based knowledge will significantly facilitate this process.

How to? Lack of understanding of route of administration

Many chronic pain patients have limited or no experience using cannabis. Certainly, some degree of education is required for inexperienced patients to become aware of their options for routes of administration and to understand how to exercise each method. This includes instructions for purchasing, grinding/milling, weighing, vaporization, joint rolling, and derivative making. Clinicians are not commonly familiar with these processes as it is not included in the current medical curriculums. However, it would be valuable for clinicians to gain knowledge in these matters to help answer patient questions and inform their prescribing practices. This education can be provided to clinicians in the future through Continuing Medical Education hours. Currently, this education is offered to patients by some licensed producers. Furthermore, clinics may have educators (ie, nurse educators and other scientifically trained staff) to educate patients on

these matters. Newly prescribed patients should also be made aware of practical and legal limitations, including barriers to traveling with the medication.

Physicians

Credibility–criminality–clinical evidence

In 2014, upward of 1,500 studies were published on cannabinoids. Knowledge is rapidly expanding and has led to a change in attitudes toward medical cannabis. A popular example of this change was the apology by Dr Sanjay Gupta in 2009 for not better appreciating cannabis as a potential therapeutic drug.⁶⁵ As we move toward greater acceptance of the medicinal benefits of cannabis, increasingly, there is a need for the establishment of evidence-based guidelines to assist clinicians in their prescribing practices in order to optimize patient care and quality of life.

Relatedly, some regional differences in the accessibility of medical cannabis have been reported.⁶⁶ Accessing medical cannabis from a friend or acquaintance was more common in the Prairies and Maritimes compared to British Columbia and Ontario,⁶⁶ suggesting reduced accessibility to authorized sources of medical cannabis in the Prairies and Maritimes. Examination of patient forums suggests that one reason for these regional differences may be a lack of physicians willing to prescribe medical cannabis in these regions. Providing physicians with evidence-based guidelines and training in prescribing practices will likely decrease such barriers to accessibility of medical cannabis.

Patient addiction

It has been shown that one in every eleven individuals (9% of individuals) consuming cannabis will become dependent on the drug.⁶⁷ Unfortunately, this statistic is based on individuals consuming all types of cannabis, irrespective of purpose for consumption (ie, medical or nonmedical) and strain. Regardless, an incidence of dependency of one per eleven is still significantly lower than those of approved pharmaceuticals commonly used for chronic pain management.⁶⁸ Monitoring for cannabis dependency is recommended for all patients.

Canadian medical cannabis regulations

In July 2001, Health Canada granted access to cannabis for medical purposes to Canadians with the support of their physicians under the Marihuana Medical Access Regulations (MMAR).⁶⁹ Under this regulation, patients were given the following options: 1) applying to access Health Canada's supply of dried marihuana under the MMAR, 2) applying for a personal-use production license, and 3) designating someone

to cultivate on their behalf with a designated-person production license. The Medical Marijuana Access program was replaced by the Marijuana for Medical Purposes Regulations (MMPR) in April 2014.⁷⁰ Following this change, production of legal medical marijuana is authorized to licensed producers. A list of the Health Canada-authorized licensed producers can be found on Health Canada's website.⁷¹ A foreign corporation could operate as a licensed producer in Canada if the "corporation that has its head office in Canada or operates a branch office in Canada and whose officers and directors are all adults".⁷²

With the introduction of the MMPR in Canada, physicians are advised to follow the guidance set forth by their provincial college. The aim of the MMPR is to treat medical cannabis like other narcotics used for medicinal purposes whenever possible. Under the MMPR, the patient must consult with a medical doctor or a qualified nurse practitioner. A signed "medical document" is submitted to a Health Canada-approved licensed commercial producer of marijuana, granting the patient access to the program. These medical documents are treated similarly to prescriptions. They must meet specific requirements, including patient name, date of birth, physician information, including license number and signature, a daily allotment in grams, and a length of time for the access not exceeding 1 year. A physician may also indicate specific strains and/or an amount of THC allowed to the patient. While there is no legal requirement for licensed producers to follow strain and THC recommendations, many will abide by the request of the physician. Dispensaries and compassion clubs are not permitted under MMPR, so appropriate steps should be taken to ensure a patient is only being referred to Health Canada-approved organizations. Once the patients purchase the medication from the company, it is shipped to their home, or that of their caretaker. Alternatively, arrangements may be made for the licensed producer to transfer the drug to the health care prescriber, from which it can then be obtained by the patients. It should be noted that Health Canada neither approves nor regulates medical cannabis like it does pharmaceutical drugs. Thus, the medical document issued by physicians for medical cannabis is distinct from, and only partially analogous to, a prescription. Instead, the medical document can be viewed as a recommendation to the medical cannabis program. In Quebec, a distinction is made that physicians should not provide such a document unless it is part of a recognized research project and only for specified conditions. Other provincial colleges will have their own requirements. A recent decision by the Supreme Court of Canada has overturned the original requirements

for licensed producers and patients to only sell and consume dried cannabis. This decision allows the sale of fresh, dried, and oil forms of cannabis to patients. Though, as of writing, no licensed producer has yet to be granted permission to sell fresh and oil alternative forms to patients.

Prescribing considerations

As mentioned, prescription and recommendation of medical cannabis at this point is largely nonspecific. Patients are recommended to the medical cannabis program but not necessarily a specific strain. Increasingly, an understanding of how specific strains of medical cannabis can offer benefit for specific ailments is appreciated by those recommending the use of medical cannabis. Unfortunately, the body of evidence supporting these practices is limited, due to an overall lack of investigation, which prevents physicians from making informed decisions to best improve the risk–benefit relationship of medical cannabis in their patients.

Many colleges recommend that Canadian physicians treat medical cannabis as they would any other prescribed narcotic drug. This often includes the use of patient–physician agreements on appropriate use and informed consent of the new medication. Physicians should also consider other following factors when recommending medical cannabis to their patients.

Amount

MMPR requires the recommending physician allot a set amount of cannabis to which a patient will have access on a daily basis. Medical cannabis programs report average patient use of between 0.68 and 1.5 g per day.^{40,73} As a physician increases the amount of medical cannabis a patient is allowed access to, so too does the risk for diversion. However, patients report using up to 10 g of cannabis per day for self-medication purposes. Both the amount the patients currently use for self-identified medical reasons and their preferred route of administration should be taken into consideration when recommending an amount of medical cannabis.

Strain selection and recommendation

Given that evidence supporting the use of specific medical cannabis strains for various pain ailments is lacking, recommending a strain type to a patient can be difficult. The decision is often determined by a number of factors, including financial concerns, potential risk to the patient, and specific goals of the patient (such as to improve sleep or to avoid feeling high). Typically, recommendations are made based on medical history, cannabis use history, and

financial barriers. Once all of these factors have been considered, a strain is selected by the clinician from a range of varieties recommended for medical use by Health Canada from authorized licensed producers. Each licensed producer produces different strains suitable for various medical purposes. Using the principles of “start low, go slow” titration, individuals with little or no experience, histories of bipolar disorder, strong familial schizophrenia, and/or a history of substance abuse begin their process with medical cannabis on a CBD-dominant strain. Patients with a history of cannabis use and no significant risk factors are initially prescribed a strain with higher THC content and maximal CBD content. If patients fail to get relief from their initial strains, an increase in the THC content is recommended in a stepwise fashion, as long as serious risk factors are not present. If risk factors are present, the risk–benefit analysis for this patient must be readdressed. Many colleges recommend indicating an amount of THC a patient would be permitted to access with a licensed producer. Unfortunately, the current regulatory environment in Canada does not require a licensed producer adhere to the recommendation. Likewise, there is rarely any guidance on prescribing strains with CBD content.

Route of administration

Many patients have concerns about medical cannabis smoke, which contains many of the same carcinogenic chemicals as tobacco smoke.⁷⁴ Ultimately, the optimal route of administration to be recommended will depend largely on the desires and capabilities of the patient.

Inhalation by vaporization is the most effective route at delivering the medicinal cannabinoid content of medical cannabis,⁷⁵ and both dried and extracted medical cannabis can be used in a vaporizer. Sometimes, vaporization can be burdensome for patients. Indeed, loading a vaporizer requires some degree of dexterity, which may be limited in certain populations of pain patients, such as those with rheumatoid arthritis and osteoarthritis. Patients may also complain of the temperature of vapor created by vaporization. Many patients require fairly extensive education regarding the use of a vaporizer.

Oral ingestion of medical cannabis typically refers to consumption of cannabis oils or edibles. These are generally produced by infusing a lipophilic substance, like an oil or butter, with cannabis, which is then used in drops or in food. Indeed, a number of recipes have become available online for the use of cannabis oil and butter in food, though some patients dislike the strong flavor. For patients with respira-

tory illnesses, the oral route is preferable. This method is limited, however, by lower absorption and bioavailability than for inhaled cannabis. Another potential concern is a lack of research on the effectiveness and safety of orally consumed cannabis for pain conditions. Given the increased latency of effect onset from orally consumed medical cannabis, patients should be cautioned to wait an adequate amount of time to feel the effects of the cannabis before readministering. While issues of dosing and effectiveness exist for orally administered cannabis, it is typically well tolerated by patients.

Sublingual tinctures are another, less common, route of administration for medical cannabis. Typically, these tinctures are extracted with ethanol, but vinegars and glycerine may also be used. The extracts are dropped under the tongue and held for a period of time sufficient to permit absorption by the branches of the lingual artery, including the sublingual and deep lingual arteries. If used properly, onset of action and bioavailability may be faster and higher for this route compared with oral administration, as is often observed with other drugs.⁷⁶ Tinctures may be a favorable option in the future, as they mitigate the dosing and bioavailability issues associated with orally ingested cannabis and eliminate issues of tolerability with inhaled cannabis. However, the use of tinctures is not widespread today, and evidence supporting the therapeutic use of tinctures is limited. Moreover, patients often complain of the taste. In Canada, there is currently a sublingual cannabinoid pharmaceutical known as Sativex. This is approved for multiple sclerosis (MS)-related neuropathic pain or spasticity and for cancer-related pain. A case series has also been published on its effectiveness for fibromyalgia.⁷⁷

Alternative routes of administration include transdermal ointments and balms, ophthalmic drops, and rectal suppositories. While rarely used, all of these routes may have therapeutic potential for patients, though little research has been done to assess this likelihood.

Follow-up frequency

When introducing a patient to medical cannabis for the first time, it is important to schedule frequent follow-ups until a strain has been selected that meets the treatment goals of both patient and physician. Since this process may require changes such as route of administration, an active follow-up schedule may be required to provide the patient with adequate knowledge to continue safely and confidently. Once a patient has been stabilized, follow-up visits should focus on monitoring for adverse reactions, including dependence.

In Canada, the medical document that is produced to allow a patient access to cannabis acts as a license. Thus, if the patients' medical document expires while they are in possession of medical cannabis, they may be open to criminal charges. The timing of a patient's follow-ups is an important nonmedical issue as well.

Contraindications

Several contraindications have been identified for medical cannabis recommendations. Due in part to the illicit nature of cannabis, research is lacking and there is a significant knowledge gap in this area, and medical cannabis recommendations should always be made with careful consideration of the current health status of the patient.

Psychosis

As previously mentioned, individuals suffering from, or at a high risk of developing, schizophrenia or other psychotic illnesses should only be recommended the use of cannabis under well-monitored conditions. The use of strains with minimal or no THC content is recommended.

Bipolar disorder

Recently, Kim et al found that cannabis use was significantly associated with lower rates of remission of bipolar spectrum patients over a 2-year follow-up period.⁷⁸ Studies have also found an association between cannabis misuse and earlier onset of bipolar disorder.⁷⁹ Thus, the use of low-THC content strains is recommended for these patients.

Cannabis allergies

It is estimated that *C. sativa* allergies are found in 8% of the general population, although the incidence may be higher among individuals who identify as users of cannabis.⁸⁰ Avoidance is recommended for patients with cannabis allergies to avoid potentially lethal anaphylaxis. However, mild rhinoconjunctivitis symptoms can be treated with antihistamines, intranasal steroids, and nasal decongestants.⁸¹ Immunotherapy has been used to treat cannabis allergies,^{82,83} but this is not common practice.

Adverse effects

Findings from the currently available research suggest that the safety profile of the short-term use of medical cannabis is acceptable.⁸⁴ A systematic review of 23 RCTs and eight observational studies of medical cannabis found that 96.6% of the adverse effects reported in the trials were not serious. The most commonly reported adverse effect was dizziness

(15.5%). Rates of serious adverse effects did not vary between the group of participants assigned to medical cannabis and controls.⁸⁴ Other commonly reported adverse effects are drowsiness, feeling faint or light headed, fatigue, headache, impaired memory, and disturbances in attention, concentration, and ability to think and make decisions.⁸⁵ However, further research on the long-term safety profile of medical cannabis use is required.^{86,87}

Case studies

Neuropathic low-back pain

A 49-year-old, single male patient reporting chronic lower back pain due to diagnoses of spinal stenosis, degenerative disc disease, and neuropathic pain including sciatica for over 20 years presented at our clinic. In-clinic recorded pain score for the patient was 9/10 on a numerical rating scale. Positive DN4 (>4/10) and Freynhagen Pain Detect Questionnaire (>19/35) scores were recorded. The patient also had diagnoses of gastroesophageal reflux disease, irritable bowel syndrome, and anxiety. At the time of meeting, the patient was using nabilone 0.25 mg daily, pregabalin 300 mg daily, ibuprofen 400–600 mg daily, omeprazole 40 mg daily, baclofen 20 mg daily, and clonazepam 0.5 mg daily. After several unsuccessful attempts at pain control using physiotherapy, chiropractic, osteopathy, acupuncture, corticosteroid injections, oxycodone, and Percocet, the patient confided he turned to illicit cannabis for pain relief on a daily basis, primarily in the evening after work.

The patient was prescribed 1 g per day of a cannabis strain containing 9% THC and 13% CBD to be administered by a vaporizer. At 60 days of follow-up, the patient's pain was lowered to a weekly average of 3/10 on a numerical rating scale. The patient also indicated he did not see a need for pregabalin, and had begun the process of lowering his daily dose. Surprisingly, the patient also reported far fewer symptoms of his irritable bowel syndrome, claiming near-remission.

Fibromyalgia – widespread neuropathic pain

A 57-year-old, married male patient reporting fibromyalgia for 5 years, and osteoarthritis, torn shoulder tendon, and spinal stenosis for over 20 years was referred to our clinic. His initial in-clinic recorded pain score was 8/10 on a numerical rating scale. The patient also had a history of severe obesity, sleep apnea, restless legs syndrome, and anxiety. Signs of neuropathic pain included widespread allodynia and positive DN4 score. At the time of meeting, the patient was taking several prescribed pain medications, including Percocet 5/325 mg as needed and Oxyneo 40 mg daily. Physiotherapy,

corticosteroid injections, codeine, and a number of anti-inflammatory medications were unsuccessful at achieving adequate analgesia. The patient was inexperienced with cannabis, except for intermittent use on weekends.

The patient was prescribed 1.5 g per day of a strain of cannabis containing 5% THC and 8% CBD to be administered by a vaporizer. After 2 weeks of trial, the patient reported a lack of success, and a strain of 12% THC was added to the other strain, with instructions to mix the strains in equal parts. At 60 days of follow-up, the patient's pain was lowered to a weekly average of 3/10 on a numerical rating scale, and he lowered his use of Percocet from four pills per day to three pills per week, on average.

MS-related neuropathic pain

A 67-year-old, single female patient reporting neuropathic pain secondary to MS diagnosis of over 20 years was referred to our clinic by her pain intervention physician. In-clinic pain score was recorded at 9/10 on a numeric rating scale. The patient was actively taking gabapentin 2,200 mg daily and celecoxib 200 mg daily. The patient could not tolerate the use of opiate medications, claiming dissatisfaction with their sedative effects. Failed pain interventions included IV lidocaine and lumbar radiofrequency ablation. The patient was naïve to cannabis.

The patient was prescribed 1 g per day of cannabis containing 2.5% THC and 5% CBD to be administered by a vaporizer. After failing to achieve adequate analgesia, a strain of 9% THC and 13% CBD was recommended to the patient. At 60 days of follow-up, the patient's pain subsided to a moderate 5/10 on a numeric rating scale, and she is planning to lower the dose of her other medications.

Conclusion

This review documents some of the relevant history and current research literature on medical cannabis. It draws attention to the key concerns in the Canadian medical system and provides updated treatment approaches to help clinicians work with their patients in achieving adequate pain control, reduced narcotic and other medication use (and their adverse effects), and enhanced quality of life. RCTs using large population samples are needed in order to identify the specific strains and concentrations that will work best with selected cohorts. Cannabis-based medicine is a rapidly emerging field of which all pain physicians need to be aware.

Disclosure

The authors report no conflicts of interest in this work.

References

- Zuardi AW. History of cannabis as a medicine: a review. *Rev Bras Psiquiatr.* 2006;28(2):153–157.
- Turcotte D, Le Dorze J-A, Esfahani F, Frost E, Gomori A, Namaka M. Examining the roles of cannabinoids in pain and other therapeutic indications: a review. *Expert Opin Pharmacother.* 2010;11(1):17–31.
- Hirst RA, Lambert DG, Notcutt WG. Pharmacology and potential therapeutic uses of cannabis. *Br J Anaesth.* 1998;81(1):77–84.
- Aldrich M. History of therapeutic cannabis. In: Mathre ML, editor. *Cannabis in Medical Practice: A Legal, Historical, and Pharmacological Overview of the Therapeutic Use of Marijuana.* Jefferson, NC: McFarland & Co.; 1997:35–55.
- Boychuk DG, Goddard G, Mauro G, Orellana MF. The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. *J Oral Facial Pain Headache.* 2015;29(1):7–14.
- Tramèr MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ.* 2001;323(7303):16–21.
- Troutt WD, DiDonato MD. Medical cannabis in Arizona: patient characteristics, perceptions, and impressions of medical cannabis legalization. *J Psychoactive Drugs.* 2015;47(4):259–266.
- Bonn-Miller MO, Boden MT, Bucossi MM, Babson KA. Self-reported cannabis use characteristics, patterns and helpfulness among medical cannabis users. *Am J Drug Alcohol Abuse.* 2014;40(1):23–30.
- Ilgen MA, Bohnert K, Kleinberg F, et al. Characteristics of adults seeking medical marijuana certification. *Drug Alcohol Depend.* 2013;132(3):654–659.
- Walsh Z, Callaway R, Belle-Isle L, et al. Cannabis for therapeutic purposes: patient characteristics, access, and reasons for use. *Int J Drug Policy.* 2013;24(6):511–516.
- Di Forti M, Morrison PD, Butt A, Murray RM. Cannabis use and psychiatric and cognitive disorders: the chicken or the egg? *Curr Opin Psychiatry.* 2007;20(3):228–234.
- Schauer GL, King BA, Bunnell RE, Promoff G, McAfee TA. Toking, vaping, and eating for health or fun: marijuana use patterns in adults, U.S., 2014. *Am J Prev Med.* 2016;50(1):1–8.
- Belle-Isle L, Hathaway A. Barriers to access to medical cannabis for Canadians living with HIV/AIDS. *AIDS Care.* 2007;19(4):500–506.
- Canadian Centre on Substance Abuse. Canadian addiction survey 2004: microdata eguide. Ottawa, ON: Canadian Centre on Substance Abuse. Available from: <http://www.ccsa.ca/Resource%20Library/ccsa-004028-2005.pdf>. Accessed August 20, 2015.
- Ebert T, Zolotov Y, Eliav S, Ginzburg O, Shapira I, Magnezi R. Assessment of Israeli physicians' knowledge, experience and attitudes towards medical cannabis: a pilot study. *Isr Med Assoc J.* 2015;17(7):437–441.
- Frank B, Serpell MG, Hughes J, Matthews JN, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ.* 2008;336(7637):199–201.
- Glass RM, Uhlenhuth EH, Hartel FW. The effects of nabilone, a synthetic cannabinoid, on anxious human volunteers [proceedings]. *Psychopharmacol Bull.* 1979;15(2):88–90.
- Lemberger L, Rubin A, Wolen R, et al. Pharmacokinetics, metabolism and drug-abuse potential of nabilone. *Cancer Treat Rev.* 1982;9 Suppl B:17–23.
- McGilveray JJ. Pharmacokinetics of cannabinoids. *Pain Res Manag.* 2005;10 Suppl A:15A–22A.
- Pertwee RG. Cannabinoid receptors and pain. *Prog Neurobiol.* 2001;63(5):569–611.
- Ben-Shabat S, Hanuš LO, Katzavian G, Gallily R. New cannabidiol derivatives: synthesis, binding to cannabinoid receptor, and evaluation of their antiinflammatory activity. *J Med Chem.* 2006;49(3):1113–1117.
- Maione S, Piscitelli F, Gatta L, et al. Non-psychoactive cannabinoids modulate the descending pathway of antinociception in anaesthetized rats through several mechanisms of action. *Br J Pharmacol.* 2011;162(3):584–596.

23. Costa B, Trovato AE, Comelli F, Giagnoni G, Colleoni M. The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. *Eur J Pharmacol*. 2007;556(1-3):75-83.
24. Niesink RJ, van Laar MW. Does cannabidiol protect against adverse psychological effects of THC? *Front Psychiatry*. 2013;16(4):130.
25. Iseger TA, Bossong MG. A systematic review of the antipsychotic properties of cannabidiol in humans. *Schizophr Res*. 2015;162(1-3):153-161.
26. De Meijer EPM, Bagatta M, Carboni A, et al. The inheritance of chemical phenotype in *Cannabis sativa* L. *Genetics*. 2003;163(1):335-346.
27. Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses*. 2006;66(2):234-246.
28. Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychoactive plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends Pharmacol Sci*. 2009;30(1):515-527.
29. Fride E, Mechoulam R. Pharmacological activity of the cannabinoid receptor agonist, anandamide, a brain constituent. *Eur J Pharmacol*. 1993;231(2):313-314.
30. Tsou K, Brown S, Sañudo-Peña MC, Mackie K, Walker JM. Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. *Neuroscience*. 1998;83(2):393-411.
31. Walker JM, Huang SM, Strangman NM, Tsou K, Sañudo-Peña MC. Pain modulation by release of the endogenous cannabinoid anandamide. *Proc Natl Acad Sci U S A*. 1999;96(21):12198-12203.
32. Wilson-Poe AR, Morgan MM, Aicher SA, Hegarty DM. Distribution of CB1 cannabinoid receptors and their relationship with mu-opioid receptors in the rat periaqueductal gray. *Neuroscience*. 2012;213:191-200.
33. Hashimoto-dani Y, Ohno-Shosaku T, Kano M. Endocannabinoids and synaptic function in the CNS. *Neuroscientist*. 2007;13(2):127-137.
34. Soltesz I, Alger BE, Kano M, et al. Weeding out bad waves: towards selective cannabinoid circuit control in epilepsy. *Nat Rev Neurosci*. 2015;16(5):264-277.
35. Richardson JD, Aanonsen L, Hargreaves KM. SR 141716A, a cannabinoid receptor antagonist, produces hyperalgesia in untreated mice. *Eur J Pharmacol*. 1997;319(2-3):R3-R4.
36. Nicholson AN, Turner C, Stone BM, Robson PJ. Effect of delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. *J Clin Psychopharmacol*. 2004;24(3):305-313.
37. Karniol IG, Shirakawa I, Kasinski N, Pfeferman A, Carlini EA. Cannabidiol interferes with the effects of delta 9-tetrahydrocannabinol in man. *Eur J Pharmacol*. 1974;28(1):172-177.
38. Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology (Berl)*. 1982;76(3):245-250.
39. Bisogno T, Hanus L, De Petrocellis L, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol*. 2001;134(4):845-852.
40. Health Canada, Controlled Substances and Tobacco Directorate. Information for health care professionals: cannabis (marihuana, marijuana) and the cannabinoids. Ottawa, ON: Health Canada, Controlled Substances and Tobacco Directorate; 2013. Available from: <http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php>. Accessed August 3, 2015.
41. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology*. 2007;68(7):515-521.
42. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology*. 2009;34(3):672-680.
43. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *CMAJ*. 2010;182(14):E694-E701.
44. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain*. 2008;9(6):506-521.
45. Wilsey B, Marcotte T, Deutsch R, et al. Low-dose vaporized cannabis significantly improves neuropathic pain. *J Pain*. 2013;14(2):136-148.
46. Corey-Bloom J, Wolfson T, Gamst A, et al. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. *CMAJ*. 2012;184(10):1143-1150.
47. Andrae MH, Carter GM, Shaparin N, et al. Inhaled cannabis for chronic neuropathic pain: a meta-analysis of individual patient data. *J Pain*. 2015;16(12):1221-1232.
48. Wiffen PJ, Derry S, Moore RA, et al. Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews. *Cochrane Database Syst Rev*. 2013;11:CD010567.
49. Birse F, Derry S, Moore RA. Phenytoin for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*. 2012;5:CD009485.
50. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database Syst Rev*. 2012;7:CD008943.
51. Corrigan R, Derry S, Wiffen PJ, Moore RA. Clonazepam for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*. 2012;5:CD009486.
52. Canadian Cancer Society. Medical marijuana and cannabinoids. 2015. Available from: <http://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/complementary-therapies/medical-marijuana-and-cannabinoids/?region=on>. Accessed August 3, 2015.
53. Huestis MA. Human cannabinoid pharmacokinetics. *Chem Biodivers*. 2007;4(8):1770-1804.
54. Agurell S, Halldin M, Lindgren JE, et al. Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man. *Pharmacol Rev*. 1986;38(1):21-43.
55. Zuurman L, Ippel AE, Moin E, van Gerven JMA. Biomarkers for the effects of cannabis and THC in healthy volunteers. *Br J Clin Pharmacol*. 2009;67(1):5-21.
56. Carter GT, Weydt P, Kyashna-Tocha M, Abrams DI. Medicinal cannabis: rational guidelines for dosing. *IDrugs*. 2004;7(5):464-470.
57. Hart CL, Ilan AB, Gevins A, et al. Neurophysiological and cognitive effects of smoked marijuana in frequent users. *Pharmacol Biochem Behav*. 2010;96(3):333-341.
58. Walsh D, Nelson KA, Mahmoud FA. Established and potential therapeutic applications of cannabinoids in oncology. *Support Care Cancer*. 2003;11(3):137-143.
59. Cone EJ, Johnson RE, Paul BD, Mell LD, Mitchell J. Marijuana-laced brownies: behavioral effects, physiologic effects, and urinalysis in humans following ingestion. *J Anal Toxicol*. 1988;12(4):169-175.
60. The Netherlands Ministry of Health Welfare and Sports. *Medicinal Cannabis, Information for Health Care Professionals*. Amsterdam, the Netherlands: The Netherlands Ministry of Health Welfare and Sports; 2008.
61. Li X-Q, Andersson TB, Ahlström M, Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome p450 activities. *Drug Metab Dispos*. 2004;32(8):821-827.
62. Spina E, Santoro V, D'Arrigo C. Clinically relevant pharmacokinetic drug interactions with second-generation antidepressants: an update. *Clin Ther*. 2008;30(7):1206-1227.
63. Karoly P, Ruehlman LS, Okun MA. Psychosocial and demographic correlates of employment vs disability status in a national community sample of adults with chronic pain: toward a psychology of pain presenteeism. *Pain Med*. 2013;14(11):1698-1707.
64. The Arthritis Society. Medical cannabis: a guide to access. 2015. Available from: <http://arthritis.ca/getmedia/99682fb5-3992-4924-895a-d5f03d16f151/Medical-Cannabis-2015-a-Guide-to-Access.pdf>. Accessed August 10, 2015.
65. Gupta S. Why I changed my mind on weed. 2013. Available from: <http://frogbuddha.com/?p=234>. Accessed July 30, 2015.
66. Belle-Isle L, Walsh Z, Callaway R, et al. Barriers to access for Canadians who use cannabis for therapeutic purposes. *Int J Drug Policy*. 2014;25(4):691-699.

67. Lopez-Quintero C, Pérez de los Cobos J, Hasin DS, et al. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug Alcohol Depend.* 2011;115(1–2):120–130.
68. Hood SD, Norman A, Hince DA, Melichar JK, Hulse GK. Benzodiazepine dependence and its treatment with low dose flumazenil. *Br J Clin Pharmacol.* 2014;77(2):285–294.
69. Health Canada. About the Marihuana Medical Access Program. 2014. Available from: <http://www.hc-sc.gc.ca/dhp-mps/marihuana/about-appropos/index-eng.php>. Accessed August 5, 2015.
70. Government of Canada. Justice Laws Website. Marihuana for Medical Purposes Regulations. 2015. Available from: <http://www.laws-lois.justice.gc.ca/eng/regulations/SOR-2013-119>. Accessed August 25, 2015.
71. Health Canada. Authorized licensed producers under the Marihuana for Medical Purposes Regulations. 2015. Available from: <http://www.hc-sc.gc.ca/dhp-mps/marihuana/info/list-eng.php>. Accessed August 5, 2015.
72. Government of Canada. Justice Laws Website. Marihuana for Medical Purposes Regulations. 2015. Available from: <http://www.laws-lois.justice.gc.ca/eng/regulations/SOR-2013-119/page-6.html>. Accessed August 10, 2015.
73. Hazekamp A, Heerdink ER. The prevalence and incidence of medicinal cannabis on prescription in the Netherlands. *Eur J Clin Pharmacol.* 2013;69(8):1575–1580.
74. Moir D, Rickert WS, Levasseur G, et al. A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. *Chem Res Toxicol.* 2008;21(2):494–502.
75. Pomahacova B, Van der Kooy F, Verpoorte R. Cannabis smoke condensate III: the cannabinoid content of vaporised Cannabis sativa. *Inhal Toxicol.* 2009;21(13):1108–1112.
76. Scavone JM, Greenblatt DJ, Friedman H, Shader RI. Enhanced bioavailability of triazolam following sublingual versus oral administration. *J Clin Pharmacol.* 1986;26(3):208–210.
77. Ko G, Wine W, Tumarkin E. Case series of fibromyalgia patients with neuropathic pain improved with the sublingual cannabinoid Sativex. *Eur J Pain.* 2007;11(S1):145–146.
78. Kim S-W, Dodd S, Berk L, et al. Impact of cannabis use on long-term remission in bipolar I and schizoaffective disorder. *Psychiatry Investig.* 2015;12(3):349–355.
79. Leite RTP, Nogueira S de O, do Nascimento JPR, et al. The use of cannabis as a predictor of early onset of bipolar disorder and suicide attempts. *Neural Plast.* 2015;2015:434127.
80. Larramendi CH, López-Matas MÁ, Ferrer A, et al. Prevalence of sensitization to Cannabis sativa. Lipid-transfer and thaumatin-like proteins are relevant allergens. *Int Arch Allergy Immunol.* 2013;162(2):115–122.
81. Ocampo TL, Rans TS. Cannabis sativa: the unconventional “weed” allergen. *Ann Allergy Asthma Immunol.* 2015;114(3):187–192.
82. Gupta BN, Mehrotra NK, Clerk SH, et al. Immunotherapy in hemp workers having respiratory complaints. *Indian J Med Sci.* 1980;34(4):72–81.
83. Kumar R, Gupta N. A case of bronchial asthma and allergic rhinitis exacerbated during Cannabis pollination and subsequently controlled by subcutaneous immunotherapy. *Indian J Allergy Asthma Immunol.* 2013;27(2):143.
84. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. *CMAJ.* 2008;178(13):1669–1678.
85. Health Canada. Consumer information – cannabis (marihuana, marijuana). 2015. Available from: <http://www.hc-sc.gc.ca/dhp-mps/marihuana/info/cons-eng.php>. Accessed August 3, 2015.
86. Degenhardt L, Hall WD. The adverse effects of cannabinoids: implications for use of medical marijuana. *CMAJ.* 2008;178(13):1685–1686.
87. Belendiuk KA, Baldini LL, Bonn-Miller MO. Narrative review of the safety and efficacy of marijuana for the treatment of commonly state-approved medical and psychiatric disorders. *Addict Sci Clin Pract.* 2015;10:10.

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Effect of Δ -9-Tetrahydrocannabinol and Cannabidiol on Nocturnal Sleep and Early-Morning Behavior in Young Adults

Anthony N. Nicholson, MD, PhD,* Claire Turner, BSc,*
Barbara M. Stone, PhD,* and Philip J. Robson, MD†

Abstract: The effects of cannabis extracts on nocturnal sleep, early-morning performance, memory, and sleepiness were studied in 8 healthy volunteers (4 males, 4 females; 21 to 34 years). The study was double-blind and placebo-controlled with a 4-way crossover design. The 4 treatments were placebo, 15 mg Δ -9-tetrahydrocannabinol (THC), 5 mg THC combined with 5 mg cannabidiol (CBD), and 15 mg THC combined with 15 mg CBD. These were formulated in 50:50 ethanol to propylene glycol and administered using an oromucosal spray during a 30-minute period from 10 PM. The electroencephalogram was recorded during the sleep period (11 PM to 7 AM). Performance, sleep latency, and subjective assessments of sleepiness and mood were measured from 8:30 AM (10 hours after drug administration). There were no effects of 15 mg THC on nocturnal sleep. With the concomitant administration of the drugs (5 mg THC and 5 mg CBD to 15 mg THC and 15 mg CBD), there was a decrease in stage 3 sleep, and with the higher dose combination, wakefulness was increased. The next day, with 15 mg THC, memory was impaired, sleep latency was reduced, and the subjects reported increased sleepiness and changes in mood. With the lower dose combination, reaction time was faster on the digit recall task, and with the higher dose combination, subjects reported increased sleepiness and changes in mood. Fifteen milligrams THC would appear to be sedative, while 15 mg CBD appears to have alerting properties as it increased awake activity during sleep and counteracted the residual sedative activity of 15 mg THC.

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A potential therapeutic benefit of the use of cannabis-based extracts in the relief of pain and other chronic symptoms

*QinetiQ Ltd, Centre for Human Sciences, Cody Technology Park, Farnborough, Hampshire, UK; †Department of Psychiatry, Warneford Hospital, Oxford, UK.

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Address correspondence and reprint requests to Prof Anthony N. Nicholson, QinetiQ Ltd, Centre for Human Sciences, Ively Road, Farnborough, Hampshire GU14 0LX, UK. E-mail: annicholson@QinetiQ.com.

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is an improvement in sleep quality. This may be due to hypnotic activity in addition to the therapeutic properties of cannabinoids.¹ Indeed, early studies indicated that sleep may be modulated.^{2–8} However, these studies used various modes of administration, involved wide dose ranges, and were carried out in subjects of variable status with respect to their use of such drugs. Furthermore, the experimental designs were not amenable to analyses that could indicate the pharmacologic activity of individual substances. In some studies, extracts were used in which, although Δ -9-tetrahydrocannabinol (THC) could be measured, there were undetermined amounts of cannabidiol (CBD) and cannabinol. Nevertheless, the impression gained from these studies was that certain doses of THC, particularly with repeated ingestion, may reduce rapid eye movement (REM) activity and increase slow-wave sleep.

We have, therefore, investigated the effect on sleep of individual cannabinoids and cannabinoids in combination. The current studies with THC and CBD have been carried out using the doses that are currently under investigation for the relief of pain. The former cannabinoid is believed to be the principal psychoactive extract of cannabis, an effect mediated via cannabinoid (CB)₁ receptors. CBD may be free of such central activity but may have useful therapeutic potential arising from its reported myorelaxant and anticonvulsant properties, in addition to the attenuation of some of the effects of THC, such as euphoria and tachycardia.^{9–12} The mechanism by which CBD exerts these effects is uncertain, as it cannot be completely explained in terms of CB₁ and CB₂ receptor binding. We have studied the effect of THC alone and in combination with CBD on the sleep process and on mood, performance, and sleep latencies during the morning of the day after administration.

METHODS

Protocol

The protocol was approved by the QinetiQ Ethics Committee, and the subjects were under medical supervision

throughout the experiment. Each was provided with detailed information on the activity and potentially adverse effects of the compounds. Subjects were required to give written informed consent in the presence of the principal investigator and were informed that they could withdraw from the experiment at any time. They were warned against driving and operating machinery during the day after each experimental night.

The subjects were required to be between 18 and 35 years and weigh between 50 and 80 kg (female) and 60 and 90 kg (male) with a body mass index not greater than 30. Information on height and race were also recorded. Inclusion in the experiment required the absence of a significant medical history. Subjects were excluded if there was a family history of a schizophrenia-like illness, a personal history of psychiatric or emotional problems, or evidence of insomnia or daytime sleepiness. An intake of >14 U of alcohol per week for females and 21 U for males, smoking >5 cigarettes or equivalent a day, or ingesting >5 beverages containing caffeine a day were also exclusion criteria. A unit of alcohol is defined in the United Kingdom as being equivalent to 7.9 g or 10 mL of pure alcohol (ethanol).

Inclusion in the experiment required the absence of clinically significant findings in the medical examination and in the associated pathology tests. These included a 12-lead electrocardiogram and measurement of blood pressure, heart rate (both supine and erect), and oral temperature. Exclusion criteria included a resting blood pressure exceeding 140 mm Hg systolic or 90 mm Hg diastolic and a resting heart rate <40 per minute. Urine analysis with a drug screen, biochemistry, hematology, and screening for hepatitis B and C were carried out. The medical examination and the pathology tests were repeated at the end of the experiment.

All subjects agreed to use barrier methods of contraception with a spermicide for the duration of the experiment and for 3 months after the completion of the experiment. They agreed that if a hormonal method was being used, it would not be discontinued during the experiment. The initial screening of the subjects included, if appropriate, a urinary pregnancy test, and this was repeated before each treatment night and on completion of the experiment.

During the time between medical screening and the first experimental night, the subjects were instructed in the techniques that would be used to measure performance and memory. Subjects reached a plateau level of performance on all tests before the first experimental night.

Subjects

There were 4 females aged between 21 and 22 (mean 21.8) years and 4 males aged between 24 and 34 (mean 28.8) years. The females weighed between 57.7 and 68.3 (mean 61.3) kg and the males weighed between 70.6 and 78.9 (mean 74.7) kg. All subjects had experienced previously the

effects of cannabis, but it was determined that this was occasional and linked to social events. Furthermore, the subjects reported that they had not used cannabis for at least 30 days before the commencement of the experiment and did not use cannabis during the experiment. This was confirmed by urinary drug screen. Subjects did not have a history of drug, alcohol, tobacco, or caffeine abuse or any history of the use of a social drug other than cannabis. This was confirmed by a urine drug screen that included that for opiates, barbiturates, benzodiazepines, cocaine, and amphetamine. The alcohol intake of the subjects did not exceed 8 U/wk in the females and 20 U/wk in the males. Two subjects were smokers—1 female (3 cigarettes per day) and 1 male (up to 4 cigarettes per day).

Experiment Design

The experiment was double-blind and placebo-controlled with a 4-way crossover design in which the acute effects of two cannabinoids (THC and a combination of THC and CBD) were observed on sleep and behavior the next day. The experiment consisted an adaptation night and 4 experimental nights. At least a week separated each experimental night. Subjects were required to retire at their normal bedtime on the nights preceding and to refrain from napping or exercise during the day before each of these nights and from exercise up to 12 hours after each night. The subjects were taken to the sleep laboratory in a chauffeur-driven car.

The adaptation night was used to familiarize the subjects with the experimental situation and to confirm that the subjects had a normal sleep pattern. As far as the adaptation night was concerned, alcohol and caffeine ingestion were prohibited for 24 hours and smoking from 5 PM before the overnight sleep.

As far as the treatment nights were concerned, alcohol was prohibited for 48 hours before and for 24 hours after drug ingestion. In addition, throughout the experiment, alcohol consumption was restricted on all other days of the week to no more than 3 U/d for males and 2 U/d for females. Caffeine was prohibited for 48 hours before and for 12 hours after, and smoking was prohibited from 5 PM before and for 12 hours after each treatment night. Subjects were also required to avoid spicy foods, Chinese food, bananas, and strong cheese during the evening before the treatment night.

On each treatment night, it was ascertained whether any of the subjects had experienced adverse effects or illnesses since the previous visit. Breath alcohol levels were measured and urine samples collected for drug screening and, if appropriate, for pregnancy testing. Negative results for the alcohol, drug, and pregnancy tests were required for the subjects to continue with the experiment. Treatments were administered during a 30-minute period from 10 PM. The subjects retired to bed at approximately 11 PM (30 minutes

after completion of treatment administration) and remained in bed until approximately 7 AM the next day (8 hours after retiring). Breakfast was provided between 7:15 and 8:15 AM. At approximately 8:30 AM (10 hours after completion of treatment administration), the subjects completed subjective assessments of sleepiness and commenced a battery of performance tasks. They left the laboratory at approximately 10:30 AM in a chauffeur-driven car after a medical practitioner had discharged them.

Treatments

There were 4 treatments: THC (15 mg) and 2 combinations of THC and CBD (5 mg THC with 5 mg CBD; 15 mg THC with 15 mg CBD), together with placebo. The drugs and placebo were prepared for the experiment by GW Pharmaceuticals plc. THC and the THC/CBD combinations were formulated in 50:50 ethanol to propylene glycol and administered by means of a pump action oromucosal spray. Each actuation was 100 μ L. The 15-mg dose of THC, the 2 combinations of THC and CBD, and the placebo were each delivered by 6 actuations during a 30-minute period given at 6-minute intervals from approximately 10 PM. Subjects were trained before the study not to swallow the liquid to maximize drug absorption through the buccal mucosa. This technique of administration has been validated.¹³

Polysomnography

The subjects slept in single, light-proofed, sound-attenuated, and temperature-controlled ($18^{\circ}\text{C} \pm 2^{\circ}\text{C}$) rooms. Silver-silver chloride electrodes were used to record electroencephalograph activity from the O_1 - A_2 and C_4 - A_1 positions, together with bilateral electrooculograms and the submental electromyogram, on to EMBLA 16-channel recorders (Flaga, Iceland). The electrocardiogram and myographic activity from the anterior tibialis muscles were also recorded throughout the night. A simulated paper speed of 10 mm/s was used and the sampling rates for the various measures were as follows: electroencephalograph, 100 Hz; electrooculograms, 100 Hz; electromyogram, 200 Hz, respectively. The records were scored manually from the screen into 30-s epochs upon completion of the experiment by one analyst according to the criteria of Rechtschaffen and Kales.¹⁴ Various measures were derived from the data for subsequent statistical analysis.

Cannabinoid Plasma Levels

A blood sample was obtained at approximately 9 PM as a control for the estimation of cannabinoid plasma levels the next morning. At approximately 8:15 AM (9.75 hours after the last actuation), a blood sample was taken for the measurement of plasma levels of the cannabinoids. Samples were collected in tubes containing lithium heparin and placed immediately into ice and water to chill before being

centrifuged at $1000 \times g$ for 10 minutes at 0°C to 4°C and stored at -20°C within 30 minutes of the sampling time. The serum levels of THC, 11-hydroxy THC (a major active metabolite of THC), and CBD were determined by a high-performance liquid chromatography method. The limit of quantification of the assay was 0.1 ng/mL.

Cardiovascular Measurements

Blood pressure and heart rate were recorded using an Accutorr Plus automatic blood pressure monitor (Datascop, Paramus, NJ) before, during, and after the 30-minute period of drug administration when the subjects were seated. The next morning on waking the subjects (at approximately 7 AM), blood pressure was measured both supine and erect.

Subjective Assessments

Before the administration of the treatments, the subjects rated their level of sleepiness using the 7-point Stanford Sleepiness Scale.¹⁵ Approximately 30 minutes after awakening, the subjects assessed the quality of their sleep and their level of alertness. The extremes of the 100-mm scales were as follows: I slept *very poorly* (0) to *very well* (100); Now I feel *very sleepy* (0) to *wide awake* (100); I fell asleep *never* (0) to *immediately* (100); after I fell asleep, I slept *very badly* (0) to *very well* (100); I wanted to sleep *much more* (0) to *much less* (100). Subjects also estimated the time to sleep onset and the sleep duration. They also rated their level of sleepiness using the Stanford Sleepiness Scale.

Measurement of Next-Day Performance, Memory, and Sleepiness

After each overnight experiment, performance was measured from approximately 8:30 AM the next morning using psychomotor and cognitive tasks, together with assessments of mood, sleepiness, and fatigue, and the electroencephalographic determination of sleep latency. The tasks were presented in the following order (with elapsed time in brackets): mood assessment (0 to 1 minute), Samn-Perelli fatigue rating (1 to 2 minutes), immediate memory word recall (2 to 4 minutes), digit symbol substitution (4 to 8 minutes), 6-letter memory recall (8 to 13 minutes), multiattribute task (MAT) battery and subjective workload ratings (13 to 63 minutes), digit memory recall (63 to 66 minutes), choice reaction time (66 to 68 minutes), sustained attention (68 to 78 minutes), delayed memory word recall (78 to 79 minutes), mood assessment (79 to 80 minutes), Samn-Perelli fatigue rating (80 to 81 minutes), Stanford Sleepiness Scale (81 to 82 minutes), and sleep latency test (82 to 107 minutes).

Digit Symbol Substitution

The subjects were presented with one of a series of 30 different sheets with 200 randomized digits (0 to 9) arranged

in 10 rows on both sides of the sheet.¹⁶ In the space below each digit, they were required to insert the appropriate symbol indicated by a code at the top of the page. They were given 2 minutes for each of the 2 sides of the sheet to complete as many substitutions as possible, and the total for each session was recorded.

Multiattribute Task Battery

The MAT battery has been developed to provide a standardized test for use in laboratory studies of performance and workload.¹⁷ The battery incorporates 4 simulation tasks that aircrew would expect to perform. The MAT battery was displayed on a screen divided into 6 windows, of which 4 were tasks: system monitoring (“dials” and “lights”), tracking, communications, and resource (fuel) management, and 2 provided information about the communications and resource management tasks. Subject responses were made using keys on a standard computer keyboard, and the battery lasted 50 minutes. Response data and reaction times were recorded for all tasks except tracking, for which the root mean error score was recorded.

Choice Reaction Time

An asterisk was displayed in 1 of 4 corners of a monitor screen, and subjects were required to respond by pressing 1 of 4 buttons in the same spatial arrangement as the asterisks on the screen.¹⁸ The task was self-paced with a total of 160 asterisks presented. Response data and reaction times were recorded.

Sustained Attention

A random sequence of letters was presented one at a time on a monitor screen at a rate of 1 each second.¹⁹ Two letters (the critical stimulus) were displayed continuously at the top left-hand corner of the screen. Subjects were required to press a button whenever the letters of the critical stimulus were presented consecutively during the random sequence. Response times and the nature of the responses (correct, missed, and wrong) were recorded.

Immediate and Delayed Word Memory Recall

The immediate word memory recall task presented a list of 16 unrelated words (2-syllable nouns with a frequency of >12 per million in general usage) on a monitor screen at a rate of 1 every 3 seconds. Immediately after the presentations, subjects were given 45 seconds to recall as many of the words as possible. Delayed memory recall was tested 76 minutes later when they were again asked to recall the words within 45 seconds. The number of words recalled and the number of words correctly recalled were recorded.

Six-Letter Memory Recall

Subjects were given 15 s to memorize a set of 6 letters. Then, a series of randomly generated letters was displayed individually on a monitor, and they were required to indicate whether the letter was contained in the memory set by pressing the appropriate button.²⁰ This procedure was repeated a further 9 times, so that a total of ten 6-letter memory sets were presented during this test. Response times and the nature of the responses (correct, missed, and wrong) were recorded during this 5-minute task.

Digit Memory Recall

Series of single-digit numbers (1 to 9) were presented simultaneously above and below a horizontal line on a monitor.²⁰ Subjects were required to memorize the digit below the line, compare it with the digit above the line in the subsequent presentation, and respond by pressing the appropriate button for “same” or “different” number. The 3-minute task was self-paced with a maximum reaction time of 2 seconds per response. Response times and the nature of the responses (correct, missed, and wrong) were recorded.

Subjective Measurements

Mood and well-being were assessed using a series of twelve 100-mm visual analogue scales.²¹ The subjects assessed their level of sleepiness using the Stanford Sleepiness Scale and rated their fatigue level against 10 separate criteria, from which a score in the range 0 (*extremely fatigued*) to 20 (*extremely alert*) was calculated.²¹ Subjects also assessed their level of workload during the MAT battery when the scale was presented on the screen at 10-minute intervals by giving a rating between 1 (*workload insignificant*) and 10 (*task abandoned—unable to apply sufficient effort*).²³

Sleep Latency Test

Subjects were instructed to lie in bed and to try to fall asleep. The electroencephalograph, electrooculograms, and electromyogram were recorded as described previously. The test was ended 20 minutes after “lights out.” Subsequently, one analyst determined the latency to stage 1 (drowsy) sleep for all recordings.

Adverse Events

Adverse events whether considered to be related to the use of the drug were recorded with details of their onset and cessation, severity, and relation to treatment.

Statistical Analysis

The statistical power for the experiment was calculated using the method of Owen.²⁴ Estimates of variance from previous studies^{25,26} were used to calculate the minimum

detectable difference between the 2 drugs for a sample of sleep and psychometric tests and for 1 subjective measurement for 8 subjects with 80% power at the 5% level of significance. The order of drug ingestion was based on a Latin-square design, balanced for carryover effects.

The data were analyzed by analysis of variance as a general test at the 5% significance level. A 1-factor model (treatment) with subjects as a random factor was used for all variables except MAT battery tracking, workload ratings, mood assessment, and the Samn-Perelli fatigue rating. For these variables, a 2-factor model (treatment and "run") was used as these variables were presented at the beginning and the end of the morning test session. Significant effects in the analysis of variance of the factors were examined using Newman-Keuls.²⁷ Planned comparisons were made between the cannabinoids and placebo using Dunnett procedure, which adjusts for multiple comparisons with a control, so that the overall error rate remains at 5%.²⁸ The assumptions of analysis of variance (homogeneity of variance, normality, and additivity) were studied by considering transformations of the raw measures using the maximum likelihood method.²⁹ Each measure was examined for a possible order effect and, if significant, was included as a linear covariate in the analyses of these measures.

A principal component analysis was carried out on the subjective assessments of mood, and 2 major varimax-rotated components were identified for analysis. The first component included measures related to lethargy, inefficiency, an inability to concentrate, dullness, sleepiness, and withdrawal. The second component included measures related to anxiety, agitation, tension, irritability, and aggression.

For the sleep latency data, on those occasions when stage 1 sleep did not occur within the 20 minutes allowed (6 of the 32 sleep latency tests), an iterative extension to a standard analysis of variance procedure was used. This method follows a standard expectation/maximization algorithm for handling data censored beyond 20-minute duration, and it overcomes a downward bias, which would otherwise be created if the value was removed altogether or if it was treated as 20 minutes.³⁰

RESULTS

Sleep, Subjective Measures, Next-Day Performance, Memory, and Sleepiness

The effects of the cannabinoids on nocturnal sleep and early-morning performance, memory, and sleepiness are given in Tables 1–3. Back-transformed means corrected for bias are shown, where appropriate, together with the transformation required.

There was no difference in the subjects' ratings of sleepiness before the administration of the 4 treatments, nor were there any differences in the subjects' assessments of

sleep onset, duration, or quality following the administration of the cannabinoids.

There were no effects of 15 mg THC on sleep. In the case of the latency to rapid eye movement sleep, although the mean data with 15 mg THC appear to be increased, the statistical analysis failed to demonstrate a significant change for the group as a whole due to the variability of the data. The next day, the subjects reported increased sleepiness 30 minutes after rising, and there were decreased latencies to early-morning sleep. The subjects also reported changes in mood. Several aspects of memory were impaired. There was a reduction in the number of words remembered correctly in the immediate and delayed recall tests.

With the concomitant administration of THC and CBD, there was evidence of decreased stage 3 sleep, and at the higher dose combination (15 mg THC with 15 mg CBD), awake time was increased. At the lower dose combination (5 mg THC and 5 mg CBD), there were no changes in mood, sleepiness, fatigue, or performance the next morning. With the higher dose combination (15 mg THC and 15 mg CBD), subjects reported increased sleepiness with fatigue and changes in mood. For both combination doses, there were no changes in performance on the memory tests, except for a reduced reaction time with the lower doses in digit recall.

Blood Pressure

Inspection of the blood pressure and pulse rate recordings did not indicate changes in blood pressure or pulse rate related to the 30-minute period of drug administration. Recordings of these measures in the morning on awakening revealed postural systolic hypotension with 15 mg THC when given alone or in combination with 15 mg CBD. There were compensatory increases in pulse rate, both supine and erect.

Cannabinoid Plasma Levels

The pharmacokinetic data showed that during the evening before drug administration, the mean serum concentrations of THC, 11-hydroxy THC, and CBD were less than the limit of quantification of the assay. The serum levels of the cannabinoids the next morning were related to the dose that had been administered the previous evening. The mean serum concentrations of THC 9.75 hours after the ingestion of 5 and 15 mg THC in combination with CBD and of 15 mg THC when ingested alone were 0.405, 1.348, and 1.170 (with standard deviations of 0.359, 0.739, and 0.700) ng/mL, respectively. Similarly, the concentrations of 11-hydroxy THC 9.75 hours after the ingestion of the 2 dose combinations of THC with CBD and of 15 mg THC alone were 0.714, 2.178, and 1.663 (with standard deviations of 0.762, 1.325, and 1.293) ng/mL, respectively. The serum

TABLE 1. Effect of the Cannabinoids (Δ -9-THC and CBD) on the Electroencephalographic Measures of Nocturnal Sleep (Means for 8 Subjects)

Measure	Transform	SE*	Placebo	15 mg THC	5 mg THC and 5 mg CBD	15 mg THC and 15 mg CBD
Total sleep time, min	log	0.3879	429.13	429.25	443.83	404.56
Sleep efficiency index [†]	log	0.2190	0.89	0.89	0.92	0.84
Sleep onset latency, min		3.9145	24.63	25.94	22.56	23.50
Latency to slow-wave sleep, min		1.5351	10.13	12.13	11.44	10.81
Latency to REM sleep, min	log	0.1487	106.56	140.13	107.44	107.44
REM to non-REM ratio	log	0.1980	0.24	0.21	0.27	0.18
Number of REM periods		0.3934	4.50	3.88	4.25	3.91
Number of awakenings		2.1375	13.63	14.13	12.50	14.25
Number of stage shifts		7.4232	106.50	103.88	100.13	100.00
Duration of wakefulness, min	log	0.3194	17.06	17.19	11.25	41.06 [‡]
Duration of stage 1 sleep, min		6.4665	45.88	43.19	44.75	42.56
Duration of stage 2 sleep, min		11.4059	234.19	233.81	235.50	233.19
Duration of stage 3 sleep, min		3.2203	32.88	28.06	24.19 [§]	23.75 [§]
Duration of stage 4 sleep, min		6.9455	40.06	53.38	48.31	49.81
Duration of stages 3 and 4, min		6.3538	72.94	81.44	72.50	73.56
Duration of REM sleep, min		11.5244	84.75	74.31	93.13	61.88

*Standard error for comparison. Where data were transformed, the SE is given on a transformed scale.

[†]Sleep efficiency index (total sleep time divided by time in bed).

[‡] $P < 0.05$ compared with 5 mg THC and 5 mg CBD.

[§] $P < 0.05$ compared with placebo.

concentrations of CBD following the ingestion of 5 and 15 mg CBD in combination with THC were 0.309 and 0.863 (with standard deviations of 0.187 and 0.425) ng/mL. There was no CBD detectable following the administration of THC alone.

Adverse Events

There were no serious adverse events and no adverse events that led to withdrawal of a subject. All 8 subjects reported at least one adverse event. Inspection of reported adverse events showed that the high dose combination of THC and CBD was likely to be associated with symptoms related to the nervous system.

DISCUSSION

It would appear that the cannabinoids, THC and CBD, when given in the doses and in the combinations used in the present study, are unlikely to have adverse clinical effects on sleep. THC would appear to be a sedative compound, whereas CBD would appear to have some alerting properties. The distinct activity of these compounds suggests that they could be complementary in clinical practice. The alerting activity of CBD may be particularly useful in the concomitant administration of THC and CBD when the therapeutic activity of both compounds is sought.

The present analysis did not provide evidence that 15 mg THC altered the sleep process, although inspection of

TABLE 2. Effect of the Cannabinoids [Δ -9-THC and CBD] on Subjective Assessments of Sleep and Sleepiness 30 Minutes After Rising, 9 Hours After Administration (Means for 8 Subjects)

Measure	SE*	Placebo	15 mg THC	5 mg THC and 5 mg CBD	15 mg THC and 15 mg CBD
Stanford Sleepiness Scale (from 1.0 = <i>wide awake</i> to 7.0 = <i>extremely sleepy</i>)	0.4157	2.38	3.75 [†]	2.88	3.71 [†]
Visual Analogue Scale (from 100 = <i>wide awake</i> to 0 = <i>very sleepy</i>)	9.7679	70.75	43.75 [†]	56.75	35.13 [‡]

*Standard error for comparison. Where data were transformed, the SE is given on a transformed scale.

[†] $P < 0.05$ compared with placebo.

[‡] $P < 0.01$ compared with placebo.

TABLE 3. Effect of the Cannabinoids [Δ -9-THC and CBD] on Performance, Memory, Mood, Subjective Sleepiness, and Sleep Latency the Next Morning 10 Hours After Administration (Means for 8 Subjects)

Measure	Transform	SE*	Placebo	15 mg THC	5 mg THC and 5 mg CBD	15 mg THC and 15 mg CBD
Digit symbol substitution						
Number of substitutions		4.5883	158.75	152.00	162.00	153.63
Choice reaction time						
Reaction time, s	Reciprocal	0.0284	0.42	0.42	0.41	0.42
Wrong, %	Square root	0.3130	2.27	3.59	3.91	3.05
Sustained attention						
Reaction time, s		0.0198	0.42	0.42	0.40	0.40
Errors (wrong and missed), %	Square root	0.5525	7.21	7.39	6.64	11.70
Immediate word recall						
No. words correctly recalled		0.8522	11.25	9.00 [†]	10.50	9.25
Delayed word recall						
No. words correctly recalled		0.9316	8.13	5.06 ^{†‡}	8.25	6.46
Six-letter memory recall						
Reaction time, s	Log	0.0373	0.93	0.96	0.88	0.96
Wrong, %	Log	0.1917	12.50	12.67	13.50	13.50
Digit memory recall						
Reaction time, s		0.0231	0.81	0.78	0.74 [†]	0.79
Errors (wrong and missed), %		0.0139	6.43	6.60	6.41	4.57
Mood (mean)						
First component [§]		0.1590	0.1821	-0.1586 ^{†‡}	0.2467	-0.2702 ^{†‡}
Second component [§]		0.2935	-0.6173	0.2670 [†]	-0.0662	0.4165 [†]
Fatigue rating (mean)						
From 20 (<i>extremely alert</i>) to 0 (<i>extremely fatigued</i>)		1.1742	11.13	8.50	9.94	7.19 [†]
Stanford sleepiness scale						
Before sleep latency test (from 1.0 = <i>wide awake</i> to 7.0 = <i>extremely sleepy</i>)		0.4613	3.25	4.13	3.88	4.50 [†]
Sleep latency						
To stage 1 sleep, min		1.3989	10.15	5.85 [†]	7.97	9.31

*Standard error for comparison. Where data were transformed, the SE is given on a transformed scale.

[†] $P < 0.05$ compared with placebo.

[‡] $P < 0.05$ compared with 5 mg THC and 5 mg CBD.

[§]The first component of mood included measures related to anxiety, agitation, tension, irritability, and aggression. Negative values indicate greater levels of these variables. The second component of mood included measures related to lethargy, inefficiency, an inability to concentrate, dullness, sleepiness, and withdrawal. Positive values indicate greater levels of these variables.

the data could suggest that in some individuals, the duration of slow-wave sleep may have been increased. However, there was evidence, the next morning, of increased sleepiness and changes in mood and of reduced latencies to early-morning sleep. Increased sleepiness and changes in mood the next day, but not the decreased latencies to early-morning sleep, were also seen when 15 mg THC was given with 15 mg CBD.

Modulation of slow-wave sleep was observed when 5 or 15 mg CBD was ingested with the same doses of THC, as there was a decrease in stage 3 sleep. It would appear possible that

CBD may increase slow-wave activity usually associated with stage 4, as there were no changes in the duration of stage 2 itself or in the combined duration of stage 2 and slow-wave sleep. This could be due to the activity of CBD alone or to its activity in combination with THC. It is also of interest that an increase in awake activity occurred with the ingestion of 15 mg CBD and 15 mg THC, but not with 5 mg CBD and 5 mg THC (or with 15 mg THC alone). This would suggest that CBD may have an alerting effect that is dependent on dose. The analysis did not provide any evidence that CBD reduced total sleep time for the group as a whole, but again, inspection of the data

could suggest that in some individuals, it was curtailed, together with rapid eye movement sleep.

In the present study, assessment of performance detected residual activity of the cannabinoids somewhat more than 10 hours after ingestion. At this time, impaired performance was limited to the effect of 15 mg THC on memory, and this observation is in broad accord with the published literature (reviewed by Ashton³¹) and with the studies of Curran et al.³² In the latter study, episodic memory and verbal learning were impaired only with 15 mg THC and not with 7.5 mg THC. These effects were contained within the 8-hour period after ingestion and were not present 24 hours after ingestion.

Although impaired memory was observed the next day when 15 mg THC was given alone overnight, there were no effects on memory when 15 mg THC was ingested with 15 mg CBD. This could be due to an alerting effect of CBD. Indeed, such an effect would be consistent with increased wakefulness during the night, absence of an effect on early-morning sleep latencies when the higher dose combination was ingested, and reduced reaction time in digit recall with the low dose combination. However, although the activity of 15 mg CBD may have counteracted the effects of 15 mg THC on memory, the subjective impression of sleepiness persisted, as did changes in mood. The possibility that CBD may counteract, at least partially, the activity of THC has been raised in connection with the psychologic effects of THC.¹²

Overall, these observations would suggest that the effects of overnight administration of THC and CBD on the sleep process and early-morning behavior are dependent on dose. This would accord with both the pharmacokinetic data and the recordings of blood pressure and pulse rate. The mean serum concentrations of these cannabinoids and of 11-hydroxy THC (a major active metabolite of THC) are clearly related to the administered dose. Persistent activity of the high dose cannabinoids when given alone or in combination was also evident from postural systolic hypotension with compensatory increases in pulse rate, both supine and erect, observed the next morning.

Clearly, the present studies on cannabis-related compounds have shown that overnight administration leads to dose-related serum concentrations and dose-related effects on the sleep process and early-morning activity. The studies have identified the discrete activities of THC and CBD related to their sedative and alerting properties and have explored the potential of sleep studies to establish dose combinations that are likely to provide the optimum balance of their activity.

It is suggested that combinations of THC and CBD are unlikely to prejudice any improvement in sleep brought about by the effects of these drugs in alleviating pain and other chronic symptoms. However, although 15 mg THC is

free of adverse effects of clinical significance on the sleep process, its activity is associated with residual effects. In this context, the coadministration of THC and CBD has advantages beyond the therapeutic benefits that both drugs may bring individually. An equal dose of CBD appears to counteract the residual effects of THC on daytime sleep latencies and memory, although the subjects may still report sleepiness.

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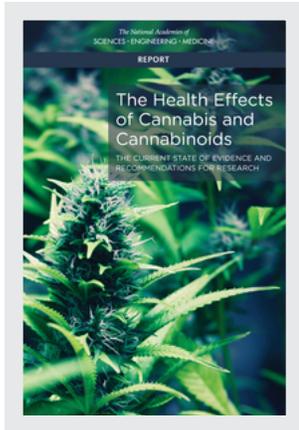
REFERENCES

1. Paton WD, Pertwee RG. The actions of cannabis in man. In: Mechoulam R, eds. *Marijuana: Chemistry, Pharmacology, Metabolism and Clinical Effects*. New York: Academic Press. 1973:288–334.
2. Pivik RT, Zarccone V, Dement WC, et al. Delta-9-Tetrahydrocannabinol and synhexl: effects on human sleep patterns. *Clin Pharmacol Ther*. 1972;13(3):426–435.
3. Hosko MJ, Kochar MS, Wang RI. Effects of orally administered delta-9-tetrahydrocannabinol in man. *Clin Pharmacol Ther*. 1973;14(3):344–352.
4. Feinberg I, Jones R, Walker J, et al. Effects of high dosage delta-9-tetrahydrocannabinol on sleep patterns in man. *Clin Pharmacol Ther*. 1975;17(4):458–466.
5. Feinberg I, Jones R, Walker J, et al. Effects of marijuana extract and tetrahydrocannabinol on electroencephalographic sleep patterns. *Clin Pharmacol Ther*. 1976;19(6):782–794.
6. Barratt ES, Beaver W, White R. The effects of marijuana on human sleep patterns. *Biol Psychiatry*. 1974;8(1):47–54.
7. Freemon FR. The effect of delta-9-tetrahydrocannabinol on sleep. *Psychopharmacology*. 1974;35:39–44.
8. Freemon FR. The effect of chronically administered delta-9-tetrahydrocannabinol upon the polygraphically monitored sleep of normal volunteers. *Drug Alcohol Depend*. 1982;10(4):345–353.
9. Consroe P, Sandyk R, Snider SR. Open label evaluation of cannabidiol in dystonic movement disorders. *Int J Neurosci*. 1986;30(4):277–282.
10. Carlini EA, Leiter JR, Tannhauser M, et al. Cannabidiol and *Cannabis sativa* extract protect mice and rats against convulsive agents. *J Pharm Pharmacol*. 1973;25:664–665.
11. Dalton WS, Martz R, Lemberger L, et al. Influence of cannabidiol on delta-9-tetrahydrocannabinol effects. *Clin Pharmacol Ther*. 1976;19(3):300–309.
12. Karniol IG, Shirakawa I, Kasinski N, et al. Cannabidiol interferes with the effects of delta-9-tetrahydrocannabinol in man. *Eur J Pharmacol*. 1974;28:172–177.
13. Guy GW, Robson PJ. A Phase I, double-blind, three-way cross-over study to assess the pharmacokinetic profile of cannabis based medicine extract (CBME) administered sublingually in variant cannabinoid ratios in normal healthy male volunteers (GWPK0215). *J Cannabis Ther*. 2003;3:121–152.
14. Rechtschaffen A, Kales A. Standardized Terminology and Scoring System for Sleep Stages of Human Subjects. U.S. Department of Health, Education and Welfare, Public Health Service, Bethesda, Maryland; 1968.
15. Hoddes E, Zarccone V, Smythe H, et al. Quantification of sleepiness: a new approach. *Psychophysiology*. 1973;10:431–436.

16. Wechsler D. A Manual for the Wechsler Adult Intelligence Scale (Revised). New York: Psychological Corporation; 1981.
17. Comstock JR, Arnegard RJ. The multi-attribute task battery for human operator workload and strategic behaviour research. *NASA Tech Memo*. 1992;104174.
18. Totterdell P, Folkard S. In situ repeated measures of affect and cognitive performance facilitated by use of a hand-held computer. *Behav Res Meth Instrum Comput*. 1992;24(4):545–553.
19. Borland RG, Rogers AS, Nicholson AN, et al. Performance overnight in shiftworkers operating a day-night schedule. *Aviat Space Environ Med*. 1986;57:241–249.
20. Shingledecker CA. A Task Battery for Applied Human Performance Assessment Research. Ohio Air Force Aerospace Medical Research Laboratories, Dayton, Ohio: Wright-Patterson Air Force Base; 1984. Report No. AFAMRL-TR-84-071.
21. Nicholson AN, Stone BM, Borland RG, et al. Adaptation to irregularity of rest and activity. *Aviat Space Environ Med*. 1984;55:102–112.
22. Samn SW, Perelli LP. Estimating Aircrew Fatigue: A Technique With Application to Airlift Operations. Brooks AFB, Tex: USAF School of Aerospace Medicine; 1982. Report SAM-TR-82-21.
23. Roscoe AH. Assessing pilot workload in flight. Neuilly Sur Seine, France: NATO Advisory Group for Aerospace Research and Development; 1984. NATO-AGARD CP No. 373 on Flight Test Technique. 12-1–12-13.
24. Owen DB. Handbook of Statistical Tables. London: Pergamon; 1962.
25. Nicholson AN, Stone BM, Turner C, et al. Antihistamines and aircrew: usefulness of fexofenadine. *Aviat Space Environ Med*. 2000; 71(1):2–6.
26. Stone BM, Turner C, Mills SL, et al. Hypnotic activity of melatonin. *Sleep*. 2000;23(5):663–669.
27. Kendall MG, Stewart A. *The advanced theory of statistics*. London: Griffin & Co.; 1967:44–46.
28. Dunnett CW. New tables for multiple comparisons with a control. *Biometrics*. 1964;20:482–491.
29. Box GEP, Cox DR. An analysis of transformations. *J R Stat Soc B*. 1964;57:24–49.
30. David HA. *Order statistics in estimation and hypothesis testing*. New York: Wiley; 1970:93–136.
31. Ashton CH. Pharmacology and effects of cannabis: a brief review. *Br J Psychiatry*. 2001;178:101–106.
32. Curran HV, Brignell C, Fletcher S, et al. Cognitive and subjective dose-response effects of acute and oral delta-9-tetrahydrocannabinol (THC) in infrequent cannabis users. *Psychopharmacology*. 2002;164(1): 61–70.

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CONTRIBUTORS

Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda; Board on Population Health and Public Health Practice; Health and Medicine Division; National Academies of Sciences, Engineering, and Medicine

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The Health Effects of Cannabis and Cannabinoids

THE CURRENT STATE OF EVIDENCE AND
RECOMMENDATIONS FOR RESEARCH

Committee on the Health Effects of Marijuana:
An Evidence Review and Research Agenda

Board on Population Health and Public Health Practice

Health and Medicine Division

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**COMMITTEE ON THE HEALTH EFFECTS OF MARIJUANA:
AN EVIDENCE REVIEW AND RESEARCH AGENDA**

- MARIE C. McCORMICK** (*Chair*), Sumner and Esther Feldberg Professor, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA
- DONALD I. ABRAMS**, Professor of Clinical Medicine, University of California, San Francisco, and Chief of Hematology–Oncology Division, Zuckerberg San Francisco General Hospital, San Francisco
- MARGARITA ALEGRÍA**, Professor, Departments of Medicine and Psychiatry, Harvard Medical School, and Chief, Disparities Research Unit, Massachusetts General Hospital, Boston
- WILLIAM CHECKLEY**, Associate Professor of Medicine, International Health, and Biostatistics, Division of Pulmonary and Critical Care, Johns Hopkins University, Baltimore, MD
- R. LORRAINE COLLINS**, Associate Dean for Research, School of Public Health and Health Professions and Professor, Department of Community Health and Health Behavior, State University of New York at Buffalo–South Campus
- ZIVA D. COOPER**, Associate Professor of Clinical Neurobiology, Department of Psychiatry, Columbia University Medical Center, New York
- ADRE J. DU PLESSIS**, Director, Fetal Medicine Institute; Division Chief of Fetal and Transitional Medicine; and Director, Fetal Brain Program, Children’s National Health System, Washington, DC
- SARAH FELDSTEIN EWING**, Professor, Department of Child and Adolescent Psychiatry, Oregon Health & Science University, Portland
- SEAN HENNESSY**, Professor of Epidemiology and Professor of Systems Pharmacology and Translational Therapeutics, University of Pennsylvania Perelman School of Medicine, Philadelphia
- KENT HUTCHISON**, Professor, Department of Psychology and Neuroscience and Director of Clinical Training, University of Colorado Boulder
- NORBERT E. KAMINSKI**, Professor, Pharmacology and Toxicology, and Director, Institute for Integrative Toxicology, Michigan State University, East Lansing
- SACHIN PATEL**, Associate Professor of Psychiatry and Behavioral Sciences, and of Molecular Physiology and Biophysics, and Director of the Division of Addiction Psychiatry, Vanderbilt University Medical Center, Nashville, TN

DANIELE PIOMELLI, Professor, Anatomy and Neurobiology, School of Medicine and Louise Turner Arnold Chair in Neurosciences, Department of Anatomy and Neurobiology, University of California, Irvine

STEPHEN SIDNEY, Director of Research Clinics, Division of Research, Kaiser Permanente Northern California, Oakland

ROBERT B. WALLACE, Irene Ensminger Stecher Professor of Epidemiology and Internal Medicine, Department of Epidemiology, University of Iowa Colleges of Public Health and Medicine, Iowa City

JOHN WILEY WILLIAMS, Professor of Medicine, Duke University Medical Center, Durham, NC

Study Staff

LEIGH MILES JACKSON, Study Director

JENNIFER A. COHEN, Program Officer

KELSEY GEISER, Research Associate (*from July 2016*)

R. BRIAN WOODBURY, Research Associate

SARA THARAKAN, Research Associate (*until July 2016*)

MATTHEW MASIELLO, Research Assistant (*from June 2016*)

MARJORIE PICHON, Senior Program Assistant (*from August 2016*)

HOPE R. HARE, Administrative Assistant

DORIS ROMERO, Financial Officer

KATHLEEN STRATTON, Scholar (Advisor)

ROSE MARIE MARTINEZ, Senior Board Director, Board on Population Health and Public Health Practice

Norman F. Grant/American Board of Obstetrics and Gynecology Fellow

BROWNSYNE TUCKER EDMONDS, Assistant Professor of Obstetrics and Gynecology, Indiana University School of Medicine, Indianapolis

Consultants

STEVEN DAVENPORT, BOTEC Analysis Corporation

TAMAR LASKY, MIE Resources, Maryland

LEANN LOCHER, LeAnn Locher and Associates

GUILLERMO MORENO-SANZ, University of California, Irvine

BRYCE PARDO, BOTEC Analysis Corporation

ROBERT POOL, Editor

Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Eric Bass, Johns Hopkins University
Jonathan P. Caulkins, Carnegie Mellon University
Mary D’Alton, Columbia University Medical Center
Eden Evins, Massachusetts General Hospital
Frank F. Furstenberg, Jr., University of Pennsylvania
Raul Gonzalez, Florida International University
Igor Grant, University of California, San Diego, School of Medicine
Mark Helfand, Oregon Health & Science University
David A. Kessler, University of California, San Francisco
John H. Krystal, Yale University School of Medicine
Aron Lichtman, Virginia Commonwealth University
Robin Mermelstein, University of Illinois at Chicago

Donald P. Tashkin, University of California, Los Angeles, David Geffen School of Medicine
Larry A. Walker, The University of Mississippi Medical Center
Mark A. Ware, McGill University

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Eric B. Larson**, Group Health Research Institute, and **Bobbie A. Berkowitz**, Columbia University Medical Center. They were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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Preface

At the time of this report's release in January 2017, 28 states and the District of Columbia have legalized cannabis for the treatment of medical conditions. Eight of these states and the District of Columbia have also legalized cannabis for recreational use. In addition to the growing availability of legalized cannabis, there has also been a rapid expansion in the types of available cannabis products, including edibles, oils, and a variety of inhaled substances. The growing acceptance, accessibility, and use of cannabis raise important public health concerns, and there is a clear need to establish what is known and what needs to be known about the health effects of cannabis use.

The committee was tasked with conducting a comprehensive review of the current evidence regarding the health effects of using cannabis and cannabis-derived products. The study was conducted in a limited time frame in order to respond to a quickly moving landscape, but as described in the report's methods section, the amount of work that this report entailed and the volume of literature reviewed clearly indicates the substantial effort involved and the importance of this issue to the committee.

In the current report, the committee presents a rigorous and thoughtful summary of the landscape of cannabis and health and puts forth recommendations to help advance the research field and better inform public health decisions. I wish to express my deepest gratitude to my fellow committee members who worked so hard and with good grace to accomplish this task. As with other National Academies of Sciences, Engineering, and Medicine reports, the work of the committee would have been

far more difficult, if not impossible, without the support of a dedicated, knowledgeable, and very hardworking National Academies staff.

Marie C. McCormick, *Chair*
Committee on the Health Effects of Marijuana:
An Evidence Review and Research Agenda

Summary

Over the past 20 years there have been substantial changes to the cannabis policy landscape. To date, 28 states and the District of Columbia have legalized cannabis for the treatment of medical conditions (NCSL, 2016). Eight of these states and the District of Columbia have also legalized cannabis for recreational use. These landmark changes in policy have markedly changed cannabis use patterns and perceived levels of risk. Based on a recent nationwide survey, 22.2 million Americans (12 years of age and older) reported using cannabis in the past 30 days, and between 2002 and 2015 the percentage of past month cannabis users in this age range has steadily increased (CBHSQ, 2016).

Despite the extensive changes in policy at the state level and the rapid rise in the use of cannabis both for medical purposes and for recreational use, conclusive evidence regarding the short- and long-term health effects (harms and benefits) of cannabis use remains elusive. A lack of scientific research has resulted in a lack of information on the health implications of cannabis use, which is a significant public health concern for vulnerable populations such as pregnant women and adolescents. Unlike other substances whose use may confer risk, such as alcohol or tobacco, no accepted standards exist to help guide individuals as they make choices regarding the issues of if, when, where, and how to use cannabis safely and, in regard to therapeutic uses, effectively.

Within this context, in March 2016, the Health and Medicine Division

BOX S-1

Statement of Task

The National Academies of Sciences, Engineering, and Medicine (the National Academies) will appoint an ad hoc committee to develop a comprehensive, in-depth review of existing evidence regarding the health effects of using marijuana and/or its constituents.

The committee will develop a consensus report with two primary sections: (1) a section of the report will summarize what can be determined about the health effects of marijuana use and, (2) a section of the report will summarize potential therapeutic uses of marijuana. The report will also provide a background overview of the cannabinoid/endocannabinoid system, history of use in the United States, and the regulation and policy landscape. In addition, the report will outline and make recommendations regarding a research agenda identifying the most critical research questions regarding the association of marijuana use with health outcomes (both risks and therapeutic) that can be answered in the short term (i.e., within a 3-year time frame) as well as any steps that should be taken in the short term to ensure that sufficient data are being gathered to answer long-term questions (e.g., appropriate questions on large population surveillance surveys, clinical data collection or other data capture, and resolution of barriers to linkage between survey data and death/morbidity registries to enable population-level morbidity and mortality effects estimates). The committee should focus on questions and consequences with the potential for the greatest public health impact, while shedding light on the characteristics of marijuana use that impact both short- and long-term health.

In conducting its work, the committee will conduct a comprehensive review of the evidence, using accepted approaches of literature search, evidence review, grading, and synthesis. Studies reviewed regarding health risks should be as broad as possible, including but not limited to epidemiology and clinical studies, and toxicology and animal studies when determined appropriate by the committee. The committee will provide summary determinations regarding causality based on strength of evidence. Both U.S. and international studies may be reviewed based upon relevance and methodological rigor.

(formerly the Institute of Medicine [IOM]¹) of the National Academies of Sciences, Engineering, and Medicine (the National Academies) was asked to convene a committee of experts to conduct a comprehensive review of the literature regarding the health effects of using cannabis and/or its constituents that had appeared since the publication of the 1999 IOM report

¹ As of March 2016, the Health and Medicine Division continues the consensus studies and convening activities previously carried out by the Institute of Medicine (IOM).

Marijuana and Medicine. The resulting Committee on the Health Effects of Marijuana consisted of 16 experts in the areas of marijuana, addiction, oncology, cardiology, neurodevelopment, respiratory disease, pediatric and adolescent health, immunology, toxicology, preclinical research, epidemiology, systematic review, and public health. The sponsors of this report include federal, state, philanthropic, and nongovernmental organizations, including the Alaska Mental Health Trust Authority; Arizona Department of Health Services; California Department of Public Health; CDC Foundation; Centers for Disease Control and Prevention (CDC); The Colorado Health Foundation; Mat-Su Health Foundation; National Highway Traffic Safety Administration; National Institutes of Health/National Cancer Institute; National Institutes of Health/National Institute on Drug Abuse; Oregon Health Authority; the Robert W. Woodruff Foundation; Truth Initiative; U.S. Food and Drug Administration; and Washington State Department of Health.

In its statement of task, the committee was asked to make recommendations for a research agenda that will identify the most critical research questions regarding the association of cannabis use with health outcomes (both harms and benefits) that can be answered in the short term (i.e., within a 3-year time frame), as well as steps that should be taken in the short term to ensure that sufficient data are being gathered to answer long-term questions. Of note, throughout the report the committee has attempted to highlight research conclusions that affect certain populations (e.g., pregnant women, adolescents) that may be more vulnerable to potential harmful effects of cannabis use. The committee's full statement of task is presented in Box S-1.

STUDY CONTEXT AND APPROACH

Over the past 20 years the IOM published several consensus reports that focused on the health effects of marijuana or addressed marijuana within the context of other drug or substance abuse topics.² The two IOM reports that most prominently informed the committee's work were *Marijuana and Health*, published in 1982, and the 1999 report *Marijuana and Medicine: Assessing the Science Base*. Although these reports differed in scope, they were useful in providing a comprehensive body of evidence upon which the current committee could build.

The scientific literature on cannabis use has grown substantially since the 1999 publication of *Marijuana and Medicine*. The committee conducted an extensive search of relevant databases, including Medline, Embase,

² See <https://www.nap.edu/search/?year=1995&rpp=20&ft=1&term=marijuana> (accessed January 5, 2017).

BOX S-2
Health Topics and Prioritized Health Endpoints
(listed in the order in which they appear in the report)

Therapeutic effects

- Chronic pain; cancer, chemotherapy-induced nausea/vomiting; anorexia and weight loss; irritable bowel syndrome; epilepsy; spasticity related to multiple sclerosis or spinal cord injury; Tourette syndrome; amyotrophic lateral sclerosis; Huntington's disease; Parkinson's disease; dystonia; dementia; glaucoma; traumatic brain injury; addiction; anxiety; depression; sleep disorders; posttraumatic stress disorder; schizophrenia and other psychoses

Cancer

- Lung cancer; head and neck cancer; testicular cancer; esophageal cancer; other cancer

Cardiometabolic risk

- Acute myocardial infarction; stroke; metabolic dysregulation, metabolic syndrome, prediabetes, and diabetes mellitus

Respiratory disease

- Pulmonary function; chronic obstructive pulmonary disorder; respiratory symptoms (including chronic bronchitis); asthma

Immunity

- Immune function; infectious disease

the Cochrane Database of Systematic Reviews, and PsycINFO, and they initially retrieved more than 24,000 abstracts that could have potentially been relevant to this study. These abstracts were reduced by limiting articles to those published in English and removing case reports, editorials, studies by “anonymous” authors, conference abstracts, and commentaries. In the end, the committee considered more than 10,700 abstracts for their relevance to this report.

Given the large scientific literature on cannabis, the breadth of the statement of task, and the time constraints of the study, the committee developed an approach that resulted in giving primacy to recently published systematic reviews (since 2011) and high-quality primary research for 11 groups of health endpoints (see Box S-2). For each health endpoint,

Injury and death

- All-cause mortality; occupational injury; motor vehicle crash; overdose injury and death

Prenatal, perinatal, and postnatal exposure to cannabis

- Pregnancy complications for the mother; fetal growth and development; neonatal conditions; later outcomes for the infant

Psychosocial

- Cognition (learning, memory, attention, intelligence); academic achievement and educational outcomes; employment and income; social relationships and other social roles

Mental health

- Schizophrenia and other psychoses; bipolar disorders, depression; suicide; anxiety; posttraumatic stress disorder

Problem cannabis use

- Cannabis use disorder

Cannabis use and abuse of other substances

- Abuse of other substances

systematic reviews were identified and assessed for quality using published criteria; only fair- and good-quality reviews were considered by the committee. The committee's conclusions are based on the findings from the most recently published systematic review and all relevant fair- and good-quality primary research published after the systematic review. Where no systematic review existed, the committee reviewed all relevant primary research published between January 1, 1999, and August 1, 2016. Primary research was assessed using standard approaches (e.g., Cochrane Quality Assessment, Newcastle–Ontario scale) as a guide.

The search strategies and processes described above were developed and adopted by the committee in order to adequately address a broad statement of task in a limited time frame while adhering to the National

Academies' high standards for the quality and rigor of committee reports. Readers of this report should recognize two important points. First, the committee was not tasked to conduct multiple systematic reviews, which would have required a lengthy and robust series of processes. The committee did, however, adopt key features of that process: a comprehensive literature search; assessments by more than one person of the quality (risk of bias) of key literature and the conclusions; prespecification of the questions of interest before conclusions were formulated; standard language to allow comparisons between conclusions; and declarations of conflict of interest via the National Academies conflict-of-interest policies. Second, there is a possibility that some literature was missed because of the practical steps taken to narrow a very large literature to one that was manageable within the time frame available to the committee. Furthermore, very good research may not be reflected in this report because it did not directly address the health endpoint research questions that were prioritized by the committee.

This report is organized into four parts and 16 chapters. Part I: Introduction and Background, Part II: Therapeutic Effects (Therapeutic Effects of Cannabis and Cannabinoids), Part III: Other Health Effects, and Part IV: Research Barriers and Recommendations. In Part II, most of the evidence reviewed in Chapter 4 derives from clinical and basic science research conducted for the specific purpose of answering an a priori question of whether cannabis and/or cannabinoids are an effective treatment for a specific disease or health condition. The evidence reviewed in Part III derives from epidemiological research that primarily reviews the effects of smoked cannabis. It is of note that several of the prioritized health endpoints discussed in Part III are also reviewed in Part II, albeit from the perspective of effects associated with using cannabis for primarily recreational, as opposed to therapeutic, purposes.

Several health endpoints are discussed in multiple chapters of the report (e.g., cancer, schizophrenia); however, it is important to note that the research conclusions regarding potential harms and benefits discussed in these chapters may differ. This is, in part, due to differences in the study design of the reviewed evidence, differences in characteristics of cannabis or cannabinoid exposure (e.g., form, dose, frequency of use), and the populations studied. As such, it is important that the reader is aware that this report was not designed to reconcile the proposed harms and benefits of cannabis or cannabinoid use across the report's chapters. In drafting the report's conclusions, the committee made an effort to be as specific as possible about the type and/or duration of cannabis or cannabinoid exposure and, where relevant, cross-referenced findings from other report chapters.

REPORT CONCLUSIONS ON THE ASSOCIATION BETWEEN CANNABIS USE AND HEALTH

From their review, the committee arrived at nearly 100 different research conclusions related to cannabis or cannabinoid use and health. Informed by the reports of previous IOM committees,³ the committee developed standard language to categorize the weight of evidence regarding whether cannabis or cannabinoid use (for therapeutic purposes) is an effective or ineffective treatment for the prioritized health endpoints of interest, or whether cannabis or cannabinoid use (primarily for recreational purposes) is statistically associated with the prioritized health

³ *Adverse Effects of Vaccines: Evidence and Causality* (IOM, 2012); *Treatment of Posttraumatic Stress Disorder: An Assessment of the Evidence* (IOM, 2008); *Veterans and Agent Orange: Update 2014* (NASEM, 2016).

BOX S-3 Weight-of-Evidence Categories

CONCLUSIVE EVIDENCE

For therapeutic effects: There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence from randomized controlled trials to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are many supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

SUBSTANTIAL EVIDENCE

For therapeutic effects: There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good-quality studies with very few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

continued

BOX S-3 Continued**MODERATE EVIDENCE**

For therapeutic effects: There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is some evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good- to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

LIMITED EVIDENCE

For therapeutic effects: There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is weak evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

NO OR INSUFFICIENT EVIDENCE TO SUPPORT THE ASSOCIATION

For therapeutic effects: There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is no or insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors.

endpoints of interest. Box S-3 describes these categories and the general parameters for the types of evidence supporting each category. For a full listing of the committee's conclusions, please see this chapter's annex.

REPORT RECOMMENDATIONS

This is a pivotal time in the world of cannabis policy and research. Shifting public sentiment, conflicting and impeded scientific research, and legislative battles have fueled the debate about what, if any, harms or benefits can be attributed to the use of cannabis or its derivatives. The committee has put forth a substantial number of research conclusions on the health effects of cannabis and cannabinoids. Based on their research conclusions, the committee members formulated four recommendations to address research gaps, improve research quality, improve surveillance capacity, and address research barriers. The report's full recommendations are described below.

Address Research Gaps

Recommendation 1: To develop a comprehensive evidence base on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), public agencies,⁴ philanthropic and professional organizations, private companies, and clinical and public health research groups should provide funding and support for a national cannabis research agenda that addresses key gaps in the evidence base. Prioritized research streams and objectives should include, but need not be limited to:

Clinical and Observational Research

- Examine the health effects of cannabis use in at-risk or under-researched populations, such as children and youth (often described as less than 18 years of age) and older populations (generally over 50 years of age), pregnant and breastfeeding women, and heavy cannabis users.
- Investigate the pharmacokinetic and pharmacodynamic properties of cannabis, modes of delivery, different concentrations, in various populations, including the dose–response relationships of cannabis and THC or other cannabinoids.
- Determine the harms and benefits associated with understudied cannabis products, such as edibles, concentrates, and topicals.
- Conduct well-controlled trials on the potential beneficial and harmful health effects of using different forms of cannabis, such

⁴ Agencies may include the CDC, relevant agencies of the National Institutes of Health (NIH), and the U.S. Food and Drug Administration (FDA).

as inhaled (smoked or vaporized) whole cannabis plant and oral cannabis.

- Characterize the health effects of cannabis on unstudied and understudied health endpoints, such as epilepsy in pediatric populations; symptoms of posttraumatic stress disorder; childhood and adult cancers; cannabis-related overdoses and poisonings; and other high-priority health endpoints.

Health Policy and Health Economics Research

- Identify models, including existing state cannabis policy models, for sustainable funding of national, state, and local public health surveillance systems.
- Investigate the economic impact of recreational and medical cannabis use on national and state public health and health care systems, health insurance providers, and patients.

Public Health and Public Safety Research

- Identify gaps in the cannabis-related knowledge and skills of health care and public health professionals, and assess the need for, and performance of, continuing education programs that address these gaps.
- Characterize public safety concerns related to recreational cannabis use and evaluate existing quality assurance, safety, and packaging standards for recreational cannabis products.

Improve Research Quality

Recommendation 2: To promote the development of conclusive evidence on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), agencies of the U.S. Department of Health and Human Services, including the National Institutes of Health and the Centers for Disease Control and Prevention, should jointly fund a workshop to develop a set of research standards and benchmarks to guide and ensure the production of high-quality cannabis research. Workshop objectives should include, but need not be limited to:

- The development of a minimum dataset for observational and clinical studies, standards for research methods and design, and guidelines for data collection methods.

- Adaptation of existing research-reporting standards to the needs of cannabis research.
- The development of uniform terminology for clinical and epidemiological cannabis research.
- The development of standardized and evidence-based question banks for clinical research and public health surveillance tools.

Improve Surveillance Capacity

Recommendation 3: To ensure that sufficient data are available to inform research on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), the Centers for Disease Control and Prevention, the Substance Abuse and Mental Health Services Administration, the Association of State and Territorial Health Officials, National Association of County and City Health Officials, the Association of Public Health Laboratories, and state and local public health departments should fund and support improvements to federal public health surveillance systems and state-based public health surveillance efforts. Potential efforts should include, but need not be limited to:

- The development of question banks on the beneficial and harmful health effects of therapeutic and recreational cannabis use and their incorporation into major public health surveys, including the National Health and Nutrition Examination Survey, National Health Interview Survey, Behavioral Risk Factor Surveillance System, National Survey on Drug Use and Health, Youth Risk Behavior Surveillance System, National Vital Statistics System, Medical Expenditure Panel Survey, and the National Survey of Family Growth.
- Determining the capacity to collect and reliably interpret data from diagnostic classification codes in administrative data (e.g., *International Classification of Diseases-10*).
- The establishment and utilization of state-based testing facilities to analyze the chemical composition of cannabis and products containing cannabis, cannabinoids, or THC.
- The development of novel diagnostic technologies that allow for rapid, accurate, and noninvasive assessment of cannabis exposure and impairment.
- Strategies for surveillance of harmful effects of cannabis for therapeutic use.

Address Research Barriers

Recommendation 4: The Centers for Disease Control and Prevention, National Institutes of Health, U.S. Food and Drug Administration, industry groups, and nongovernmental organizations should fund the convening of a committee of experts tasked to produce an objective and evidence-based report that fully characterizes the impacts of regulatory barriers to cannabis research and that proposes strategies for supporting development of the resources and infrastructure necessary to conduct a comprehensive cannabis research agenda. Committee objectives should include, but need not be limited to:

- Proposing strategies for expanding access to research-grade marijuana, through the creation and approval of new facilities for growing and storing cannabis.
- Identifying nontraditional funding sources and mechanisms to support a comprehensive national cannabis research agenda.
- Investigating strategies for improving the quality, diversity, and external validity of research-grade cannabis products.

REFERENCES

- CBHSQ (Center for Behavioral Health Statistics and Quality). 2016. Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health (HHS Publication No. SMA 15-4927, NSDUH Series H-50). <https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2015/NSDUH-FFR1-2015/NSDUH-FFR1-2015.pdf> (accessed December 5, 2016).
- IOM (Institute of Medicine). 2008. *Treatment of posttraumatic stress disorder: An assessment of the evidence*. Washington, DC: The National Academies Press.
- IOM. 2012. *Adverse effects of vaccines: Evidence and causality*. Washington, DC: The National Academies Press.
- NASEM (National Academies of Sciences, Engineering, and Medicine). 2016. *Veterans and agent orange: Update 2014*. Washington, DC: The National Academies Press.
- NCSL (National Conference of State Legislatures). 2016. State medical marijuana laws. November 9. <http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx> (accessed November 21, 2016).

ANNEX

Report Conclusions⁵*Chapter 4 Conclusions—Therapeutic Effects of Cannabis and Cannabinoids***There is conclusive or substantial evidence that cannabis or cannabinoids are effective:**

- For the treatment of chronic pain in adults (cannabis) (4-1)
- As antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)

There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols) (4-19)

There is limited evidence that cannabis or cannabinoids are effective for:

- Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids) (4-4a)
- Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)
- Improving symptoms of Tourette syndrome (THC capsules) (4-8)
- Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol) (4-17)
- Improving symptoms of posttraumatic stress disorder (nabilone; a single, small fair-quality trial) (4-20)

⁵ Numbers in parentheses correspond to chapter conclusion numbers.

There is limited evidence of a statistical association between cannabinoids and:

- Better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage (4-15)

There is limited evidence that cannabis or cannabinoids are ineffective for:

- Improving symptoms associated with dementia (cannabinoids) (4-13)
- Improving intraocular pressure associated with glaucoma (cannabinoids) (4-14)
- Reducing depressive symptoms in individuals with chronic pain or multiple sclerosis (nabiximols, dronabinol, and nabilone) (4-18)

There is no or insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are an effective treatment for:

- Cancers, including glioma (cannabinoids) (4-2)
- Cancer-associated anorexia cachexia syndrome and anorexia nervosa (cannabinoids) (4-4b)
- Symptoms of irritable bowel syndrome (dronabinol) (4-5)
- Epilepsy (cannabinoids) (4-6)
- Spasticity in patients with paralysis due to spinal cord injury (cannabinoids) (4-7b)
- Symptoms associated with amyotrophic lateral sclerosis (cannabinoids) (4-9)
- Chorea and certain neuropsychiatric symptoms associated with Huntington's disease (oral cannabinoids) (4-10)
- Motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia (cannabinoids) (4-11)
- Dystonia (nabilone and dronabinol) (4-12)
- Achieving abstinence in the use of addictive substances (cannabinoids) (4-16)
- Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis (cannabidiol) (4-21)

Chapter 5 Conclusions—Cancer

There is moderate evidence of *no* statistical association between cannabis use and:

- Incidence of lung cancer (cannabis smoking) (5-1)
- Incidence of head and neck cancers (5-2)

There is limited evidence of a statistical association between cannabis smoking and:

- Non-seminoma-type testicular germ cell tumors (current, frequent, or chronic cannabis smoking) (5-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- Incidence of esophageal cancer (cannabis smoking) (5-4)
- Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer (5-5)
- Subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (parental cannabis use) (5-6)

Chapter 6 Conclusions—Cardiometabolic Risk

There is limited evidence of a statistical association between cannabis use and:

- The triggering of acute myocardial infarction (cannabis smoking) (6-1a)
- Ischemic stroke or subarachnoid hemorrhage (6-2)
- Decreased risk of metabolic syndrome and diabetes (6-3a)
- Increased risk of prediabetes (6-3b)

There is no evidence to support or refute a statistical association between *chronic effects* of cannabis use and:

- The increased risk of acute myocardial infarction (6-1b)

*Chapter 7 Conclusions—Respiratory Disease***There is substantial evidence of a statistical association between cannabis smoking and:**

- Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term cannabis smoking) (7-3a)

There is moderate evidence of a statistical association between cannabis smoking and:

- Improved airway dynamics with acute use, but not with chronic use (7-1a)
- Higher forced vital capacity (FVC) (7-1b)

There is moderate evidence of a statistical association between the cessation of cannabis smoking and:

- Improvements in respiratory symptoms (7-3b)

There is limited evidence of a statistical association between cannabis smoking and:

- An increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use (occasional cannabis smoking) (7-2a)

There is no or insufficient evidence to support or refute a statistical association between cannabis smoking and:

- Hospital admissions for COPD (7-2b)
- Asthma development or asthma exacerbation (7-4)

*Chapter 8 Conclusions—Immunity***There is limited evidence of a statistical association between cannabis smoking and:**

- A decrease in the production of several inflammatory cytokines in healthy individuals (8-1a)

There is limited evidence of *no* statistical association between cannabis use and:

- The progression of liver fibrosis or hepatic disease in individuals with viral hepatitis C (HCV) (daily cannabis use) (8-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- Other adverse immune cell responses in healthy individuals (cannabis smoking) (8-1b)
- Adverse effects on immune status in individuals with HIV (cannabis or dronabinol use) (8-2)
- Increased incidence of oral human papilloma virus (HPV) (regular cannabis use) (8-4)

Chapter 9 Conclusions—Injury and Death

There is substantial evidence of a statistical association between cannabis use and:

- Increased risk of motor vehicle crashes (9-3)

There is moderate evidence of a statistical association between cannabis use and:

- Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal (9-4b)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- All-cause mortality (self-reported cannabis use) (9-1)
- Occupational accidents or injuries (general, nonmedical cannabis use) (9-2)
- Death due to cannabis overdose (9-4a)

Chapter 10 Conclusions—Prenatal, Perinatal, and Neonatal Exposure

There is substantial evidence of a statistical association between maternal cannabis smoking and:

- Lower birth weight of the offspring (10-2)

There is limited evidence of a statistical association between maternal cannabis smoking and:

- Pregnancy complications for the mother (10-1)
- Admission of the infant to the neonatal intensive care unit (NICU) (10-3)

There is insufficient evidence to support or refute a statistical association between maternal cannabis smoking and:

- Later outcomes in the offspring (e.g., sudden infant death syndrome, cognition/academic achievement, and later substance use) (10-4)

Chapter 11 Conclusions—Psychosocial

There is moderate evidence of a statistical association between cannabis use and:

- The impairment in the cognitive domains of learning, memory, and attention (acute cannabis use) (11-1a)

There is limited evidence of a statistical association between cannabis use and:

- Impaired academic achievement and education outcomes (11-2)
- Increased rates of unemployment and/or low income (11-3)
- Impaired social functioning or engagement in developmentally appropriate social roles (11-4)

There is limited evidence of a statistical association between *sustained abstinence from cannabis use* and:

- Impairments in the cognitive domains of learning, memory, and attention (11-1b)

*Chapter 12 Conclusions—Mental Health***There is substantial evidence of a statistical association between cannabis use and:**

- The development of schizophrenia or other psychoses, with the highest risk among the most frequent users (12-1)

There is moderate evidence of a statistical association between cannabis use and:

- Better cognitive performance among individuals with psychotic disorders and a history of cannabis use (12-2a)
- Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use) (12-4)
- A small increased risk for the development of depressive disorders (12-5)
- Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users (12-7a)
- Increased incidence of suicide completion (12-7b)
- Increased incidence of social anxiety disorder (regular cannabis use) (12-8b)

There is moderate evidence of *no* statistical association between cannabis use and:

- Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders (12-2c)

There is limited evidence of a statistical association between cannabis use and:

- An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders (12-2b)
- The likelihood of developing bipolar disorder, particularly among regular or daily users (12-3)
- The development of any type of anxiety disorder, except social anxiety disorder (12-8a)
- Increased symptoms of anxiety (near daily cannabis use) (12-9)

- Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (12-11)

There is no evidence to support or refute a statistical association between cannabis use and:

- Changes in the course or symptoms of depressive disorders (12-6)
- The development of posttraumatic stress disorder (12-10)

Chapter 13 Conclusions—Problem Cannabis Use

There is substantial evidence that:

- Stimulant treatment of attention deficit hyperactivity disorder (ADHD) during adolescence is *not* a risk factor for the development of problem cannabis use (13-2e)
- Being male and smoking cigarettes are risk factors for the progression of cannabis use to problem cannabis use (13-2i)
- Initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use (13-2j)

There is substantial evidence of a statistical association between:

- Increases in cannabis use frequency and the progression to developing problem cannabis use (13-1)
- Being male and the severity of problem cannabis use, but the recurrence of problem cannabis use does not differ between males and females (13-3b)

There is moderate evidence that:

- Anxiety, personality disorders, and bipolar disorders are *not* risk factors for the development of problem cannabis use (13-2b)
- Major depressive disorder is a risk factor for the development of problem cannabis use (13-2c)
- Adolescent ADHD is *not* a risk factor for the development of problem cannabis use (13-2d)

- Being male is a risk factor for the development of problem cannabis use (13-2f)
- Exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use (13-2g)
- Neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use (13-2h)
- During adolescence the frequency of cannabis use, oppositional behaviors, a younger age of first alcohol use, nicotine use, parental substance use, poor school performance, anti-social behaviors, and childhood sexual abuse are risk factors for the development of problem cannabis use (13-2k)

There is moderate evidence of a statistical association between:

- A persistence of problem cannabis use and a history of psychiatric treatment (13-3a)
- Problem cannabis use and increased severity of posttraumatic stress disorder symptoms (13-3c)

There is limited evidence that:

- Childhood anxiety and childhood depression are risk factors for the development of problem cannabis use (13-2a)

Chapter 14 Conclusions—Cannabis Use and the Abuse of Other Substances

There is moderate evidence of a statistical association between cannabis use and:

- The development of substance dependence and/or a substance abuse disorder for substances, including alcohol, tobacco, and other illicit drugs (14-3)

There is limited evidence of a statistical association between cannabis use and:

- The initiation of tobacco use (14-1)
- Changes in the rates and use patterns of other licit and illicit substances (14-2)

*Chapter 15 Conclusions—Challenges and Barriers in Conducting Cannabis Research***There are several challenges and barriers in conducting cannabis and cannabinoid research, including**

- There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research (15-1)
- It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use (15-2)
- A diverse network of funders is needed to support cannabis and cannabinoid research that explores the beneficial and harmful health effects of cannabis use (15-3)
- To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed (15-4)

Part I

Introduction and Background

1

Introduction

Over the past 20 years, significant changes have taken place in the policy landscape surrounding cannabis legalization, production, and use. To date, 28 states and the District of Columbia have legalized cannabis for the treatment of medical conditions (NCSL, 2016). Eight of these states and the District of Columbia have also legalized cannabis for recreational use. These landmark changes in policy have markedly changed cannabis use patterns and perceived levels of risk. Based on a recent nationwide survey, 22.2 million Americans (12 years of age and older) reported using cannabis in the past 30 days, and between 2002 and 2015 the percentage of past month cannabis users in this age range has steadily increased (CBHSQ, 2016).

Despite this reported rapid rise in the use of cannabis, both for medical purposes and for recreational use, conclusive evidence regarding the short- and long-term health effects of cannabis use remains elusive. While a myriad of studies have examined cannabis use in all its various forms (Calabria et al., 2010; Whiting et al., 2015, 2016; WHO, 2016), often these research conclusions are not appropriately synthesized, translated for, or communicated to policy makers, health care providers, state health officials, or other stakeholders who have been charged with influencing and enacting policies, procedures, and laws related to cannabis use. Unlike other substances whose use may confer risk, such as alcohol or tobacco, no accepted standards for the safe use or appropriate doses are available to help guide individuals as they make choices regarding the issues of if, when, where, and how to use cannabis safely and, in regard to therapeutic

tic uses, effectively (Freeman et al., 2014; Marsot et al., 2016). Moreover, studying the potential health impacts of cannabis presents its own set of unique challenges. Current challenges include the existence of certain regulations and policies that restrict access to cannabis products suited for research purposes (e.g., Schedule 1 status; regulatory approvals), the limited availability of funding for comprehensive cannabis research, and crosscutting methodological challenges. Additionally, researchers are often unable to obtain the necessary quantity, quality, or type of cannabis product to address cutting-edge public health research questions.

STUDY CHARGE

Shifting public sentiment, conflicting and impeded scientific research, and legislative battles have fueled the debate about what, if any, harms or benefits can be attributed to the use of cannabis or its derivatives. In March 2016 the Health and Medicine Division¹ of the National Academies of Sciences, Engineering, and Medicine (the National Academies) was asked to convene a committee of experts to conduct a comprehensive review of literature regarding the health consequences of using cannabis or its constituents that had appeared since the publication of the 1999 Institute of Medicine (IOM) report *Marijuana and Medicine* (IOM, 1999). In addition, the committee was asked to make recommendations for a research agenda that will identify the most critical research questions regarding the association of cannabis use with health outcomes (both harms and benefits) that can be answered in the short term (i.e., within a 3-year time frame), as well as steps that should be taken in the short term to ensure that sufficient data are being gathered to answer long-term questions. Of note, throughout this report the committee has attempted to highlight research conclusions that affect certain populations (e.g., pregnant women, adolescents) that may be at greater risk for potential adverse effects of cannabis use. The committee's full statement of task is presented in Box 1-1.

The resulting Committee on the Health Effects of Marijuana included experts in the areas of marijuana, addiction, oncology, cardiology, neurodevelopment, pulmonary, pediatric and adolescent health, immunology, toxicology, preclinical research, epidemiology, systematic review, and public health. (See Appendix E for the biographical sketches of committee members.)

In conducting its work, the committee met six times from March 2016 through December 2016. In conjunction with two of those meet-

¹ As of March 2016, the Health and Medicine Division continues the consensus studies and convening activities previously carried out by the Institute of Medicine (IOM).

BOX 1-1

Statement of Task

The National Academies of Sciences, Engineering, and Medicine (the National Academies) will appoint an ad hoc committee to develop a comprehensive, in-depth review of existing evidence regarding the health effects of using marijuana and/or its constituents.

The committee will develop a consensus report with two primary sections: (1) a section of the report will summarize what can be determined about the health effects of marijuana use and, (2) a section of the report will summarize potential therapeutic uses of marijuana. The report will also provide a background overview of the cannabinoid/endocannabinoid system, history of use in the United States and the regulation and policy landscape. In addition, the report will outline and make recommendations regarding a research agenda identifying the most critical research questions regarding the association of marijuana use with health outcomes (both risks and therapeutic) that can be answered in the short term (i.e., within a 3-year time frame) as well as any steps that should be taken in the short term to ensure that sufficient data are being gathered to answer long-term questions (e.g., appropriate questions on large population surveillance surveys, clinical data collection or other data capture, and resolution of barriers to linkage between survey data and death/morbidity registries to enable population-level morbidity and mortality effects estimates). The committee should focus on questions and consequences with the potential for the greatest public health impact, while shedding light on the characteristics of marijuana use that impact both short- and long-term health.

In conducting its work, the committee will conduct a comprehensive review of the evidence, using accepted approaches of literature search, evidence review, grading and synthesis. Studies reviewed regarding health risks should be as broad as possible, including but not limited to epidemiology and clinical studies, and toxicology and animal studies when determined appropriate by the committee. The committee will provide summary determinations regarding causality based on strength of evidence. Both U.S. and international studies may be reviewed based upon relevance and methodological rigor.

ings, the committee held half-day public information-gathering sessions which allowed the committee to hear from study sponsors, experts, and other stakeholders. These discussions helped to inform the committee's deliberations.

Sponsors of this report include federal, state, philanthropic, and non-governmental organizations. These include the Alaska Mental Health Trust Authority; Arizona Department of Health Services; California Department of Public Health; CDC Foundation; Centers for Disease Control and Prevention (CDC); The Colorado Health Foundation; Mat-Su Health Foundation; National Highway Traffic Safety Administration;

National Institutes of Health/National Cancer Institute; National Institutes of Health/National Institute on Drug Abuse; Oregon Health Authority; the Robert W. Woodruff Foundation; Truth Initiative; U.S. Food and Drug Administration; and the Washington State Department of Health.

STUDY CONTEXT AND APPROACH

Over the past 20 years the IOM has published several consensus reports that focused on the health effects of marijuana or addressed marijuana within the context of other drug or substance abuse topics.² Two IOM reports that most prominently informed the committee's work were *Marijuana and Health* (IOM, 1982), and the 1999 report *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999). Although these reports differed in scope, they were useful in providing a comprehensive body of evidence upon which the current committee could build.

Marijuana and Health (IOM, 1982) was commissioned by the former Secretary of Health and Human Services and the former director of the National Institutes of Health, Joseph Califano, Jr., and Donald S. Fredrickson, respectively. The study's committee was appointed to (1) analyze the potential hazards of marijuana use on user safety and health, (2) analyze data concerning the therapeutic value of marijuana, (3) assess the federal research programs, (4) identify new research directions, and (5) draw conclusions that would assist future policy decision making. The authoring committee concluded that there was evidence indicating that marijuana has a broad range of psychological and biological effects, some of which under certain conditions are harmful to human health, but there was a substantial lack of definitive evidence to characterize the seriousness of harm. The committee's major conclusion was that "what little we know for certain about the effects of marijuana on human health—and all that we have reason to suspect—justifies serious national concern" (IOM, 1982, p. 5). The committee's major recommendation called for an intensification and more comprehensive research effort into the effects of marijuana on the health of the American people.

In 1997 the White House Office of National Drug Control Policy contracted with the IOM to conduct a scientific review of available literature to determine the potential health benefits and risks of marijuana and its constituent cannabinoids. The resulting report, *Marijuana and Medicine* (IOM, 1999), offered several conclusions and recommendations (see Box 1-2) on the effects of isolated cannabinoids, the efficacy of cannabinoid drugs, the influence of psychological effects on therapeutic effects,

² See <https://www.nap.edu/search/?year=1995&rpp=20&ft=1&term=marijuana> (accessed July 2016).

BOX 1-2***Marijuana and Medicine: Assessing the Science Base (1999)***
Conclusions and Recommendations**Conclusions:**

- At this point, our knowledge about the biology of marijuana and cannabinoids allows us to make some general conclusions:
 - Cannabinoids likely have a natural role in pain modulation, control of movement, and memory.
 - The natural role of cannabinoids in immune systems is likely multifaceted and remains unclear.
 - The brain develops tolerance to cannabinoids.
 - Animal research demonstrates the potential for dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine, or nicotine.
 - Withdrawal symptoms can be observed in animals but appear to be mild compared to opiates or benzodiazepines, such as diazepam (Valium).
- The different cannabinoid receptor types found in the body appear to play different roles in normal human physiology. In addition, some effects of cannabinoids appear to be independent of those receptors. The variety of mechanisms through which cannabinoids can influence human physiology underlies the variety of potential therapeutic uses for drugs that might act selectively on different cannabinoid systems.
- Scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily tetrahydrocannabinol (THC), for pain relief, control of nausea and vomiting, and appetite stimulation; smoked marijuana, however, is a crude THC delivery system that also delivers harmful substances.
- The psychological effects of cannabinoids, such as anxiety reduction, sedation, and euphoria, can influence their potential therapeutic value. Those effects are potentially undesirable for certain patients and situations and beneficial for others. In addition, psychological effects can complicate the interpretation of other aspects of the drug's effect.
- Numerous studies suggest that marijuana smoke is an important risk factor in the development of respiratory disease. A distinctive marijuana withdrawal syndrome has been identified, but it is mild and short lived. The syndrome includes restlessness, irritability, mild agitation, insomnia, sleep disturbance, nausea, and cramping.
- Present data on drug use progression neither support nor refute the suggestion that medical availability would increase drug abuse. However, this question is beyond the issues normally considered for medical uses of drugs and should not be a factor in evaluating the therapeutic potential of marijuana or cannabinoids.

continued

BOX 1-2 Continued**Recommendations:**

- Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoid research should include, but not be restricted to, effects attributable to THC alone.
- Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.
- Psychological effects of cannabinoids such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.
- Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent.
- Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than 6 months), should be conducted in patients with conditions for which there is reasonable expectation of efficacy, should be approved by institutional review boards, and should collect data about efficacy.
- Short-term use of smoked marijuana (less than 6 months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:
 - failure of all approved medications to provide relief has been documented,
 - the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs,
 - such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness,
 - and involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.

SOURCE: IOM, 1999.

physiological risks, marijuana dependence and withdrawal, marijuana as a “gateway drug,” and the use of smoked marijuana.

The scientific literature on cannabis use has grown substantially since the publication of *Marijuana and Medicine* in 1999. The current committee conducted an extensive search of relevant databases, including Medline, Embase, the Cochrane Database of Systematic Reviews, and PsycINFO,



FIGURE 1-1 Summary of the committee’s process.

and they initially retrieved more than 24,000 abstracts for articles published since the 1999 report that could potentially be relevant to this study. These abstracts were reduced by limiting articles to those published in English and removing case reports, editorials, studies by “anonymous” authors, conference abstracts, and commentaries. In the end, the committee considered more than 10,700 abstracts for their relevance to this report. (See Appendix B for details.)

The methodological approach taken by the committee to conduct this comprehensive literature review and meet the objectives outlined in the Statement of Task is detailed in Appendix B and briefly described here. Given the large scientific literature on cannabis, the breadth of the statement of task, and the time constraints of the study, the committee developed an approach that resulted in giving primacy to recently published systematic reviews (since 2011) and high-quality primary research that studied 1 or more of 11 groups of health endpoints (see Figure 1-1 and Box 1-3). For each health endpoint, systematic reviews were identified and assessed for quality using methods adapted from published criteria (Whiting et al., 2016); only reviews that were assessed by the committee as being of good or fair quality were considered in this comprehensive review. The committee’s conclusions are based on the findings from the most recently published systematic review and all relevant primary literature that was determined to be fair and good quality that was published after the most recent systematic review. Where no systematic review existed, the committee reviewed all relevant primary research from January 1, 1999, through August 1, 2016. Primary research was evaluated using global assessments of the quality of available studies guided by standard approaches and methodologies (Cochrane Quality Assessment [Higgins et al., 2011], Newcastle–Ontario scale [Wells et al., 2014]). Any deviations from this approach are noted in the relevant chapters. For a comprehensive description of the committee’s approach to evaluating the available literature, please refer to Appendix B.

BOX 1-3
Health Topics and Prioritized Health Endpoints
(listed in the order in which they appear in the report)

Therapeutic effects

- Chronic pain; cancer, chemotherapy-induced nausea/vomiting; anorexia and weight loss; irritable bowel syndrome; epilepsy; spasticity related to multiple sclerosis or spinal cord injury; Tourette syndrome; amyotrophic lateral sclerosis; Huntington's disease; Parkinson's disease; dystonia; dementia; glaucoma; traumatic brain injury; addiction; anxiety; depression; sleep disorders; posttraumatic stress disorder; schizophrenia and other psychoses

Cancer

- Lung cancer; head and neck cancer; testicular cancer; esophageal cancer; other cancer

Cardiometabolic risk

- Acute myocardial infarction; stroke; metabolic dysregulation, metabolic syndrome, prediabetes, and diabetes mellitus

Respiratory disease

- Pulmonary function; chronic obstructive pulmonary disorder; respiratory symptoms (including chronic bronchitis); asthma

Immunity

- Immune function; infectious disease

Informed by the reports of previous IOM committees,³ the committee developed standard language to categorize the weight of evidence regarding whether cannabis or cannabinoid use (for therapeutic purposes) is an effective or ineffective treatment for the prioritized health endpoints of interest, or whether cannabis or cannabinoid use (primarily for recreational purposes) is statistically associated with the prioritized health endpoints of interest. Box 1-4 describes these categories and the general parameters for the types of evidence supporting each category. The committee used these weight-of-evidence categories in their conclusions.

³ *Adverse Effects of Vaccines: Evidence and Causality* (IOM, 2012); *Treatment of Posttraumatic Stress Disorder: An Assessment of the Evidence* (IOM, 2008); *Veterans and Agent Orange: Update 2014* (NASEM, 2016).

Injury and death

- All-cause mortality; occupational injury; motor vehicle crash; overdose injury and death

Prenatal, perinatal, and postnatal exposure to cannabis

- Pregnancy complications for the mother; fetal growth and development; neonatal conditions; later outcomes for the infant

Psychosocial

- Cognition (learning, memory, attention, intelligence); academic achievement and educational outcomes; employment and income; social relationships and other social roles

Mental health

- Schizophrenia and other psychoses; bipolar disorders, depression; suicide; anxiety; posttraumatic stress disorder

Problem cannabis use

- Cannabis use disorder

Cannabis use and abuse of other substances

- Abuse of other substances

The search strategies and processes described above were developed and adopted by the committee in order to adequately address a broad statement of task in a limited time frame while adhering to the National Academies high standards for the quality and rigor of committee reports.

First, the committee was not tasked with conducting multiple systematic reviews, which would have implied a lengthy and robust series of processes. The committee adopted key features of that process; however, a comprehensive literature search; assessments by more than one person of the quality (risk of bias) of key literature and the conclusions; pre-specification of the questions of interest before conclusions were formulated; standard language to allow comparisons between conclusions; and

BOX 1-4
Weight-of-Evidence Categories

CONCLUSIVE EVIDENCE

For therapeutic effects: There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence from randomized controlled trials to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are many supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

SUBSTANTIAL EVIDENCE

For therapeutic effects: There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good-quality studies with very few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

MODERATE EVIDENCE

For therapeutic effects: There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

declarations of conflict of interest via the National Academies' conflict-of-interest policies.

Second, there is a possibility that some literature was missed because of the practical steps taken to narrow a very large literature to one that was manageable within the time frame available to the committee. Furthermore, some very good research may not have been reviewed in this report because it did not directly address the specific health endpoint questions formulated by the committee.

For other health effects: There is some evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good- to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

LIMITED EVIDENCE

For therapeutic effects: There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is weak evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

NO OR INSUFFICIENT EVIDENCE TO SUPPORT THE ASSOCIATION

For therapeutic effects: There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is no or insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors.

Special Considerations for the Report

Biological Plausibility

After careful consideration, the committee chose not to attempt to review basic, nonhuman research in order to attempt to bolster evidence for identified health outcomes from cannabis exposure. This policy was, in part, dictated by the time constraints available for crafting this report. Also, while basic research is in the end critical for understanding health outcome mechanisms and suggesting new and innovative interventions,

it often cannot explain the large number of null findings, the frequent variation among human study outcomes, the adverse clinical effects seen in some studies, nor the diversity in host susceptibility to cannabis exposure. Given the methodologic variation in the studies reviewed, as well as potential deficiencies in study design and execution, the committee focused its attention and energy on identifying high-quality studies with the best information and lowest risk of bias as the way to ensure that report findings and conclusions were as informative and relevant as possible. In those instances where cannabis-disease associations seemed relatively secure and evidence-based, the committee believed that the findings would have clinical and public health importance even in the absence of supporting basic studies. Similarly, for those experimental studies where causation could be more explicitly determined—mostly in the area of therapeutics—these findings, if sufficiently robust and replicable, were deemed to stand on their own whether or not bolstered with mechanistic or biologically plausible underpinnings.

Considerations of Observational Studies

The vast majority of the systematic reviews, meta-analyses, and primary literature reviewed in Part III: Other Health Effects consists of observational studies. This is in contrast to the literature base in other fields such as therapeutics (discussed in Part II: Therapeutic Effects). As such, it was not possible to restrict the literature reviews to those that synthesized evidence from randomized clinical trials (RCTs). The methodology used for systematic reviews and meta-analysis originates in the synthesis of data from RCTs, where methodology is highly standardized and structured. The synthesis of observational studies presents some challenges that have not been fully met, arising, in part, out of the greater variety in study design.

Exposure measurement is always an additional concern when evaluating comprehensive reviews of observational studies. Assessment of cannabis exposure is particularly challenging because of its illegal status (in most settings) and the reliance on self-report. Inherent difficulties in accurately assessing the exposure in terms of dose, specific type of cannabis product used, mode of intake, duration, frequency, and other variables result in the variability in definitions used to operationalize cannabis exposure. Additionally, observational studies often have to contend with confounders related to polysubstance use, which obscures the ability to answer questions about the effects of “cannabis only” on the health effects. Moreover, in some cases, samples included different populations (i.e., adolescents versus adults), cannabis-use history (i.e., chronic versus

acute), and patterns of use (i.e., frequency, dose, quantity)—all of which provide mixed or inconsistent evidence as to the effects of cannabis on a specific outcome. Additional limitations include a lack of longitudinal assessments and small study cohorts.

There is also a concern about the broad reporting standards across cannabis research fields. For example, several systematic reviews on cognition discussed in the report's Psychosocial chapter did not consistently describe the methods for scoring the evidence for each endpoint. That is, the reviews include scores of the strength and consistency of the evidence for each outcome, but they provided less information about issues such as study design and statistical analyses. As a result, the committee found that the reviews did not include the conventional data generally found within quantitatively-based systematic examinations of a topic, or such as would be found in meta-analytic reviews. Reasons for this may include variations in study methodologies, instrumentation, populations, or research designs.

Despite these special considerations regarding the use of systematic reviews, meta-analyses, and primary literature of observational studies, the committee determined that using recent good- or fair-quality systematic reviews was the most appropriate approach to adequately address the committee's broad statement of task and comprehensive, prioritized research questions while maintaining a high standard for quality and rigor. For additional information on these considerations, please see Box 11-2 in Chapter 11 (Psychosocial) and Box 12-2 in Chapter 12 (Mental Health).

Comparing Harms and Benefits of Cannabis Use

Several health endpoints are discussed in multiple chapters of the report (e.g., cancer, schizophrenia); however, it is important to note that the research conclusions regarding potential harms and benefits discussed in these chapters may differ. This is, in part, due to differences in the study design of the reviewed evidence, differences in characteristics of cannabis or cannabinoid exposure (e.g., form, dose, frequency of use), and the populations studied. As such, it is important that the reader is aware that this report was not designed to reconcile the proposed harms and benefits of cannabis or cannabinoid use across the report's chapters. In drafting the report's conclusions, the committee made an effort to be as specific as possible about the type and/or duration of cannabis or cannabinoid exposure and, where relevant, cross-referenced findings from other report chapters.

Key Definitions

The terms “marijuana” and “cannabis” are often used interchangeably, particularly within the United States; however, these are two separate entities. Cannabis is a broad term that can be used to describe organic products (e.g., cannabinoids,⁴ marijuana,⁵ hemp⁶) derived from the *Cannabis sativa* plant. These products exist in various forms and are used for a number of different purposes (e.g., medical, industrial, recreational). Given its broad potential, the all-encompassing word “cannabis” has been adopted as the standard terminology within scientific and scholarly communities. The committee uses the term “cannabis” rather than “marijuana” throughout this report.

The committee notes the existence of “cannabimimetic agents” (often referred to as “K2” or “Spice”) which are made up of dried plant matter sprayed with synthetic chemicals that mimic the effect of THC by interacting with cannabinoid receptors in the brain (King, 2014). At the request of the study sponsors, nontherapeutic synthetic cannabinoids are not considered in this study.

REPORT ORGANIZATION

This report is organized into four parts and 16 chapters. Part I: Introduction and Background (Chapters 1–3) provides an overview of the origin, purpose, and organization of the report, as well as essential information on cannabis and cannabis-derived medications and products, and the history and current state of federal and state cannabis policy. In addition to this Introduction (Chapter 1), Chapter 2 (Cannabis) reviews the biology of cannabis and its constituent compounds, exploring the biochemistry of the marijuana plant, its derivatives, and the different routes of administration. Additionally, this chapter provides an overview of synthetic versions of cannabis, including U.S. Food and Drug Administration–approved medicinal synthetics and manufactured cannabis (street drugs such as K2, Spice). Chapter 3 (Cannabis: Prevalence of Use, Regulation, and Current Policy Landscape) provides an overview of cannabis use in the United States and reviews policy related to cannabis legislation.

⁴ Cannabinoids are a group of active chemical compounds found in cannabis. Among the more than 100 different types of cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD) (Small, 2015).

⁵ In general, marijuana refers only to parts of the plant or derivative products that contain substantial levels of tetrahydrocannabinol (THC), the chemical compound that is found in the highest concentrations in the cannabis plant and which is primarily responsible for the plant’s intoxicative qualities (Small, 2015).

⁶ Under U.S. law, cannabis plants with very low levels of THC (not more than 0.3 percent) are not considered marijuana but instead “industrial hemp” (Small, 2015).

Part II: Therapeutic Effects (Chapter 4—Therapeutic Effects of Cannabis and Cannabinoids) discusses the health effects of cannabis and cannabinoids used for therapeutic purposes in relation to the most commonly reported conditions for medical cannabis use (in states where usage is legal), as well as the current qualifying ailments recognized by state medical marijuana programs. Most of the evidence reviewed in this chapter derives from clinical and basic science research conducted for the specific purpose of answering an a priori question of whether cannabis and/or cannabinoids are an effective treatment for a specific disease or health condition. The vast majority of these studies examined the potential therapeutic effect of cannabinoids (e.g., FDA-approved synthetics) rather than smoked cannabis.

Part III: Other Health Effects (Chapters 5–14) discusses the health effects of cannabis and/or cannabis-derived products used for primarily recreational and other nontherapeutic purposes. Most of the evidence reviewed in Part III derives from epidemiological research primarily focusing on smoked cannabis. It is of note that several of the prioritized health conditions discussed in Part III are also reviewed in Part II, albeit from the perspective of effects associated with using cannabis for primarily recreational, as opposed to therapeutic, purposes. A bulleted list of chapter highlights are included in the introduction of the chapters in Part II and Part III of the report.

Within Part III, the effects of cannabis use on cancer incidence are discussed in Chapter 5. Chapter 6 addresses cardiometabolic risks of cannabis use, including effects on acute myocardial infarction, stroke, and metabolic effects—metabolic dysregulation, metabolic syndrome, prediabetes, and diabetes mellitus. Respiratory disease—pulmonary function, chronic obstructive pulmonary disease, respiratory symptoms including chronic bronchitis, and asthma—are discussed in Chapter 7. Immunity and infection are discussed in Chapter 8. The effects of cannabis use on overall mortality, overdose death, employment injuries, and motor vehicle crashes are reviewed in Chapter 9 (Injury and Death). Prenatal, perinatal, and neonatal effects are discussed in Chapter 10. Psychosocial effects, including the effects of cannabis on learning, memory, attention, academic achievement, employment and income, and social relationships and social roles are discussed in Chapter 11, and mental health conditions, including schizophrenia and other psychosis, bipolar disorder, depression, suicide, anxiety, and posttraumatic stress disorder are discussed in Chapter 12. Chapter 13 discusses problem cannabis use, including cannabis use disorder, and the abuse of other substances is discussed in Chapter 14.

Part IV: Research Barriers and Recommendations (Chapters 15–16) reviews the regulatory barriers and methodological challenges that hinder cannabis research, and recommends the actions necessary to successfully

implement a comprehensive cannabis research agenda. Chapter 15 provides an overview of barriers to studying cannabis, including regulatory, policy, and financial, as well as of methodological challenges, and Chapter 16 outlines the committee's proposed research agenda, detailing both short-term and long-term objectives.

Appendixes A–E contain the report glossary, details about the committee's search strategy, systematic reviews considered in this report, open session agendas, and biographical sketches of committee and staff members.

REFERENCES

- Calabria, B., L. Degenhardt, W. Hall, and M. Lynskey. 2010. Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. *Drug and Alcohol Review* 29(3):318–330.
- CBHSQ (Center for Behavioral Health Statistics and Quality). 2016. *Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health*. <https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2015/NSDUH-FFR1-2015/NSDUH-FFR1-2015.pdf> (accessed January 3, 2017).
- Freeman, T. P., C. J. Morgan, C. Hindocha, G. Schafer, R. K. Das, and H. V. Curran. 2014. Just say “know”: How do cannabinoid concentrations influence users' estimates of cannabis potency and the amount they roll in joints? *Addiction* 109(10):1686–1694.
- Higgins, J. P. T., D. G. Altman, P. C. Gøtzsche, P. Jüni, D. Moher, A. D. Oxman, J. Savović, K. F. Schulz, L. Weeks, J. A. C. Sterne, Cochrane Bias Methods Group, and Cochrane Statistical Methods Group. 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343:d5928.
- IOM (Institute of Medicine). 1982. *Marijuana and health*. Washington, DC: National Academy Press.
- IOM. 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC: National Academy Press.
- IOM. 2008. *Treatment of posttraumatic stress disorder: An assessment of the evidence*. Washington, DC: The National Academies Press.
- IOM. 2012. *Adverse effects of vaccines: Evidence and causality*. Washington, DC: The National Academies Press.
- King, L.A. 2014. Legal controls on cannabimimetics: An international dilemma? *Drug Testing and Analysis* 6(1-2):80–87.
- Marsot, A., C. Audebert, L. Attolini, B. Lacarelle, J. Micallef, and O. Blin. 2016. Comparison of cannabinoid concentrations in plasma, oral fluid and urine in occasional cannabis smokers after smoking cannabis cigarette. *Journal of Pharmacy and Pharmaceutical Sciences* 19(3):411–422.
- NASEM (National Academies of Sciences, Engineering, and Medicine). 2016. *Veterans and agent orange: Update 2014*. Washington, DC: The National Academies Press.
- NCSL (National Conference of State Legislatures). 2016. *State medical marijuana laws*. November 9. <http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx> (accessed November 21, 2016).
- Small, E. 2015. Evolution and classification of *Cannabis sativa* (marijuana, hemp) in relation to human utilization. *The Botanical Review* 81(3):189–294.

- Wells, G. A., B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, and P. Tugwell. 2014. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed November 2, 2016).
- Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidtkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.
- Whiting, P., J. Savovic, J. P. T. Higgins, D. M. Caldwell, B. C. Reeves, B. Shea, P. Davies, J. Kleijnen, R. Churchill, and the ROBIS Group. 2016. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. *Journal of Clinical Epidemiology* 69:225–234.
- WHO (World Health Organization). 2016. *The Health and Social Effects of Nonmedical Cannabis Use*. Geneva, Switzerland: WHO Document Production Services.

2

Cannabis

HISTORY OF CANNABIS

Cannabis sativa is one of the world's oldest cultivated plants (Russo, 2007). Although the earliest written records of the human use of cannabis date from the 6th century B.C. (ca. 2,600 cal BP), existing evidence suggests that its use in Europe and East Asia started in the early Holocene (ca. 8,000 cal BP) (Long et al., 2016). Many 19th-century practitioners ascribed medicinal properties to cannabis after the drug found its way to Europe during a period of colonial expansion into Africa and Asia. For example, William B. O'Shaughnessy, an Irish physician working at the Medical College and Hospital in Calcutta, first introduced cannabis (Indian hemp) to Western medicine as a treatment for tetanus and other convulsive diseases (O'Shaughnessy, 1840). At approximately the same time, French physician Jean-Jacques Moreau de Tours experimented with the use of cannabis preparations for the treatment of mental disorders (Moreau de Tours, 1845). Soon after, in 1851, cannabis was included in the 3rd edition of the *Pharmacopoeia of the United States* (USP). Subsequent revisions of the USP described in detail how to prepare extracts and tinctures of dried cannabis flowers to be used as analgesic, hypnotic, and anticonvulsant (Russo, 2007; U.S. Pharmacopoeial Convention, 1916). Growing concerns about cannabis resulted in the outlawing of cannabis in several states in the early 1900s and federal prohibition of the drug in 1937 with the passage of the Marihuana Tax Act. In response to these concerns, in 1942 the American Medical Association removed cannabis from the 12th edition of *U.S. Pharmacopeia* (IOM, 1999).

THE CANNABIS PLANT

Cannabis cultivars are considered as part of one genus, *Cannabis*, family Cannabaceae, order Urticales (Kuddus et al., 2013). Two accepted genera of Cannabaceae are *Cannabis* and *Humulus* (hops). There is, however, an ongoing debate concerning the taxonomic differentiation within the *Cannabis* genus (Laurson, 2015). On the basis of genetic variations, a multitypic genus with at least two putative species, *Cannabis sativa* and *Cannabis indica*, has been proposed by some researchers (Clarke and Merlin, 2015; Hillig, 2005). Other researchers have suggested a unique species *Cannabis sativa* with the genetic differences explained by variations at both the subspecies and the variety level or at a biotype level of putative taxa (Small, 2015).

Chemical Constituents of Cannabis

To date, more than 104 different cannabinoids¹ have been identified in cannabis (ElSohly and Gul, 2014). Other compounds identified include terpenoids, flavonoids, nitrogenous compounds, and more common plant molecules (American Herbal Pharmacopoeia, 2013). Among these, Δ^9 -tetrahydrocannabinol (THC) has received the most attention for being responsible for the intoxicated state sought after by recreational cannabis users, owing to its ability to act as a partial agonist² for type-1 cannabinoid (CB₁) receptors. Cannabinoids exist mainly in the plant as their carboxylic precursors (Δ^9 -tetrahydrocannabinolic acid [THCA] and cannabidiolic acid [CBDA]) and are decarboxylated by light or heat while in storage or when combusted (Grotenhermen, 2003). Δ^9 -THC is synthesized within the glandular trichomes present in the flowers, leaves, and bracts of the female plant. It shares a common precursor, olivetolic acid, with another quantitatively important constituent of *Cannabis sativa*, cannabidiol (CBD), which is the most abundant cannabinoid in hemp (see Figure 2-1). For this reason, the genetic profile and relative level of expression of the enzymes responsible for their synthesis (genotype), namely THCA synthase and CBDA synthase, determine the chemical composition of a particular cultivar (chemotype).

Cannabis plants typically exhibit one of the three main different chemotypes based on the absolute and relative concentrations of Δ^9 -THCA and CBDA (see Table 2-1), which makes it possible to distinguish among the Δ^9 -THC-type, or drug-type; the intermediate-type; and the CBD-type

¹ Cannabinoids are a group of psychoactive chemical compounds found in the cannabis plant.

² Partial agonists are ligands that interact with their receptors to produce a level of response that is less than the response to full agonists.

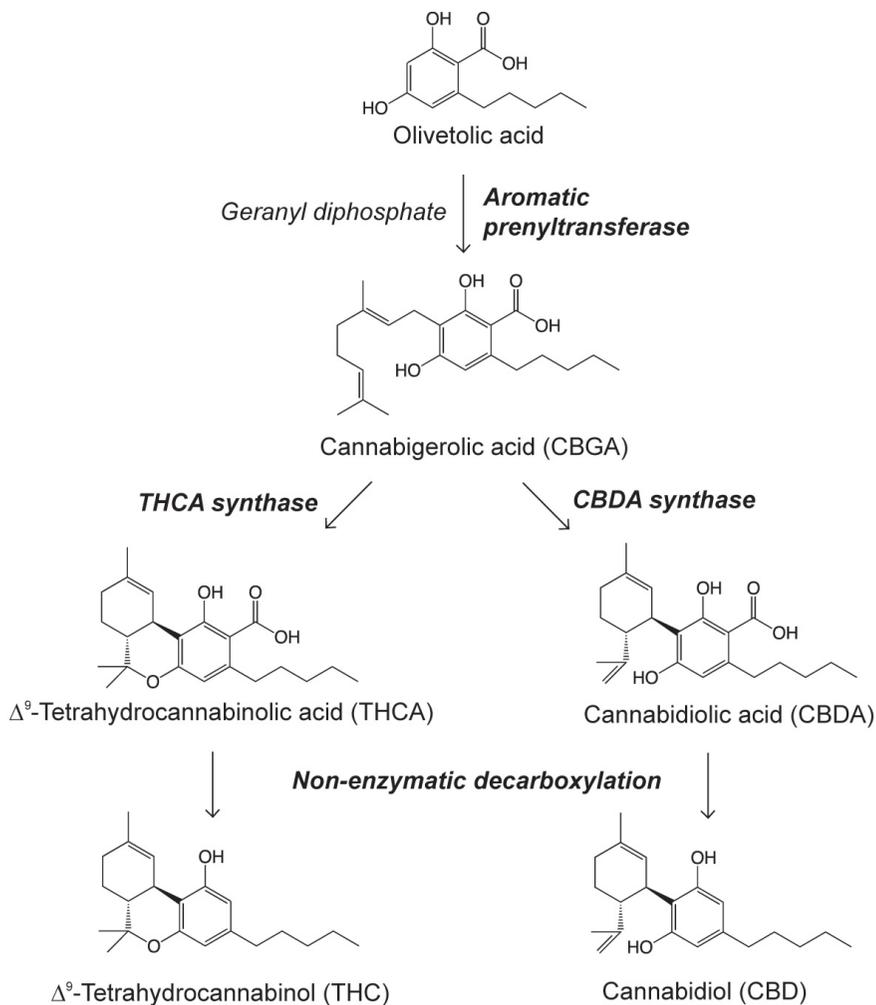


FIGURE 2-1 Synthetic pathway of the main cannabinoids, Δ^9 -THC and CBD, from the common precursor, olivetol.

cannabis plants grown for fiber (industrial hemp) or seed oil in which the content of Δ^9 -THC does not exceed 0.3 percent on a dry-weight basis (Chandra et al., 2013). CBD is pharmacologically active, however, and, therefore, classifying cannabis in terms of drug- and fiber-producing seems inaccurate. Both THC- and CBD-types are considered drug-types, and both cultivars could theoretically be exploited to produce fiber.

TABLE 2-1 Cannabis Phenotypes

Chemotype	Δ^9 -THC	CBD	CBD: Δ^9 -THC ratio
THC-type	0.5–15%	0.01–0.16%	<0.02
Hybrid	0.5–5%	0.9–7.3%	0.6–4
CBD-type	0.05–0.7%	1.0–13.6%	>5

NOTE: THCA-predominant strains can yield more than 25 percent Δ^9 -THC; specifically selected CBDA clones can yield up to 20 percent CBD.

SOURCE: Modified from Galal et al., 2009.

Pharmacological Properties of Δ^9 -THC

In a series of studies conducted in the late 1930s and early 1940s, Roger Adams and coworkers isolated cannabinol and CBD from hemp oil and then isomerized CBD into a mixture of two tetrahydrocannabinols with “marihuana-like” physiological activity in dogs, proving their structure except for the final placement of one double bond (Adams et al., 1940a,b). Two years later, tetrahydrocannabinol was first isolated from cannabis resin (Wollner et al., 1942). In 1964, thanks to the development of such potent analytical techniques as nuclear magnetic resonance imaging, Gaoni and Mechoulam were able to identify the position of this elusive double bond, thus resolving the final structure of Δ^9 -THC (Gaoni and Mechoulam, 1964).

In the late 1980s William Devane and Allyn Howlett first postulated the existence of cannabinoid receptors by showing how synthetic molecules designed to mimic the actions of Δ^9 -THC were able to bind a selective site in brain membranes, thus inhibiting the intracellular synthesis of cyclic adenosine monophosphate (cAMP) through a G protein–mediated mechanism (Devane et al., 1988). The mapping of cannabinoid-binding sites in the rat brain (Herkenham et al., 1990) and the molecular cloning of the first cannabinoid receptor gene (Matsuda et al., 1990) subsequently corroborated this hypothesis. Three years later, a second G protein–coupled cannabinoid receptor was cloned from a promyelocytic cell line and termed CB₂ (Munro et al., 1993).

Both CB₁ and CB₂ signal through the transducing G proteins, G_i and G_o, and their activation by Δ^9 -THC or other agonists causes the inhibition of adenylyl cyclase activity, the closing of voltage-gated calcium channels, the opening of inwardly rectifying potassium channels, and the stimulation of mitogen-activated protein kinases such as extracellular signal–regulated kinases (ERKs) and focal adhesion kinases (FAKs) (Mackie, 2006).

The expression pattern of CB₁ receptors in brain structures correlates with the psychoactive effects of cannabis. In mammals, high concen-

trations of CB₁ are found in areas that regulate appetite, memory, fear extinction, motor responses, and posture such as the hippocampus, basal ganglia, basolateral amygdala, hypothalamus, and cerebellum (Mackie, 2006). CB₁ is also found in a number of nonneural tissues, including the gastrointestinal tract, adipocytes, liver, and skeletal muscle. In addition to CB₁, the brain also contains a small number of CB₂ receptors, although this subtype is mainly expressed in macrophages and macrophage-derived cells such as microglia, osteoclasts, and osteoblasts (Mackie, 2006).

Pharmacological Properties of Cannabidiol

Cannabidiol was first isolated from hemp oil in 1940 (Adams et al., 1940a) and its structure predicted by chemical methods (Adams et al., 1940b); its fine structure was determined in later studies (Mechoulam and Shvo, 1963). CBD lacks the cannabis-like intoxicating properties of Δ⁹-THC and, for this reason, has been traditionally considered non-psychoactive. CBD displays very low affinity for CB₁ and CB₂ cannabinoid receptors (Thomas et al., 2007), but it might be able to negatively modulate CB₁ via an allosteric mechanism (Laprairie et al., 2015)³; however, CBD can interfere with the deactivation of the endocannabinoid molecule anandamide, by targeting either its uptake or its enzymatic degradation, catalyzed by fatty acid amide hydrolase (FAAH), which could indirectly activate CB₁ (De Petrocellis et al., 2011; Elmes et al., 2015) (see Box 2-1).

CBD is also a known agonist of serotonin 5-HT_{1A} receptors (Russo et al., 2005) and transient receptor potential vanilloid type 1 (TRPV1) receptors (Bisogno et al., 2001). It can also enhance adenosine receptor signaling by inhibiting adenosine inactivation, suggesting a potential therapeutic role in pain and inflammation (Carrier et al., 2006). The antioxidant and anti-inflammatory properties of this compound may explain its potential neuroprotective actions (Scuderi et al., 2009). Irrespective of the mechanism of action, there is evidence that CBD could potentially be exploited in the treatment and symptom relief of various neurological disorders such as epilepsy and seizures (Hofmann and Frazier, 2013; Jones et al., 2010), psychosis (Leweke et al., 2016), anxiety (Bergamaschi et al., 2011), movement disorders (e.g., Huntington's disease and amyotrophic lateral sclerosis) (de Lago and Fernandez-Ruiz, 2007; Iuvone et al., 2009), and multiple sclerosis (Lakhan and Rowland, 2009).

³ Allosteric modulators are ligands that indirectly influence the effects of an agonist or inverse agonist at a target receptor. Allosteric modulators bind to a site distinct from that of the orthosteric agonist binding site.

BOX 2-1 Endocannabinoids and Their Signaling Systems

There are two endocannabinoids, 2-archidonoylglycerol (2-AG) and anandamide.

2-AG

2-AG is generated by the enzymatic activity of a membrane-associated diacylglycerol lipase (DGL), which converts Sn2-arachidonic acid containing diacylglycerols into 2-AG (see Figure 2-2). Two isoforms of DGL, alpha and beta, have been identified. The alpha isoform generates 2-AG utilized during neuronal development and for synaptic communication between neurons, while the beta isoform may contribute to both brain development and inflammation. The activity of DGL- α is regulated by intracellular calcium, glutathione, and cellular localization, and via posttranslational modification. Once produced, 2-AG can act via both CB₁ and CB₂ receptors to exert a range of biological effects in central and peripheral cells.

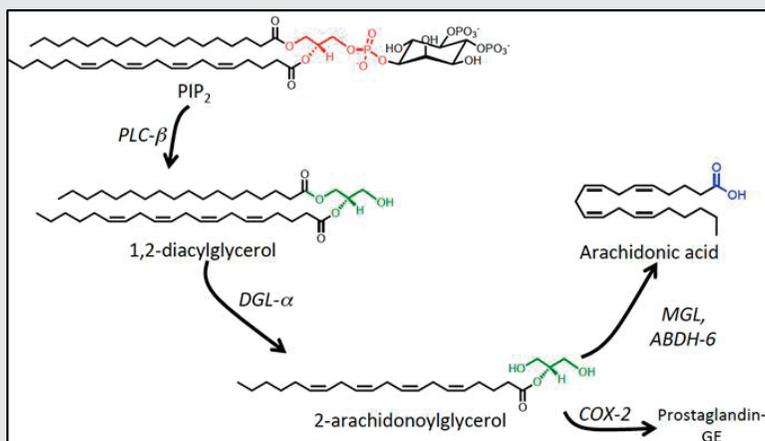


FIGURE 2-2 Pathways of 2-AG formation and deactivation.

2-AG is primarily degraded by monoacylglycerol lipase (MGL) into free arachidonic acid and glycerol. In the central nervous system (CNS), the free arachidonic acid generated by MGL-mediated hydrolysis of 2-AG may serve as a precursor for the generation of prostaglandins by cyclooxygenases. The activity of MGL can be regulated by posttranslational modification (e.g., sulfenylation). There is also evidence that 2-AG can be oxygenated by cyclooxygenase-2 to generate prostaglandin glycerols.

Anandamide

The formation of anandamide involves two steps (see Figure 2-3). The first consists of the transfer of arachidonic acid from phosphatidylcholine (PC) to phosphatidylethanolamine (PE). This reaction is catalyzed by the *N*-acyltransferase PLA2G4E and yields a diverse group of *N*-arachidonoyl-substituted PE species (NAPEs). The second step is the cleavage of NAPEs to produce anandamide and may be mediated by either NAPE-specific phospholipase D (NAPE-PLD) or alpha/beta-hydrolase domain-4 (ABHD-4). PLA2G4E may represent the rate-limiting step for anandamide formation, though additional work is needed to confirm this possibility. After release into the extracellular milieu, anandamide is captured by neurons and glia through carrier-mediated transport and is subsequently hydrolyzed to arachidonic acid by fatty acid amide hydrolase (FAAH), a postsynaptic serine hydrolase expressed throughout the CNS. In microglia, anandamide might be also degraded by the lysosomal cysteine hydrolase, *N*-acylethanolamine acid amidase (NAAA).

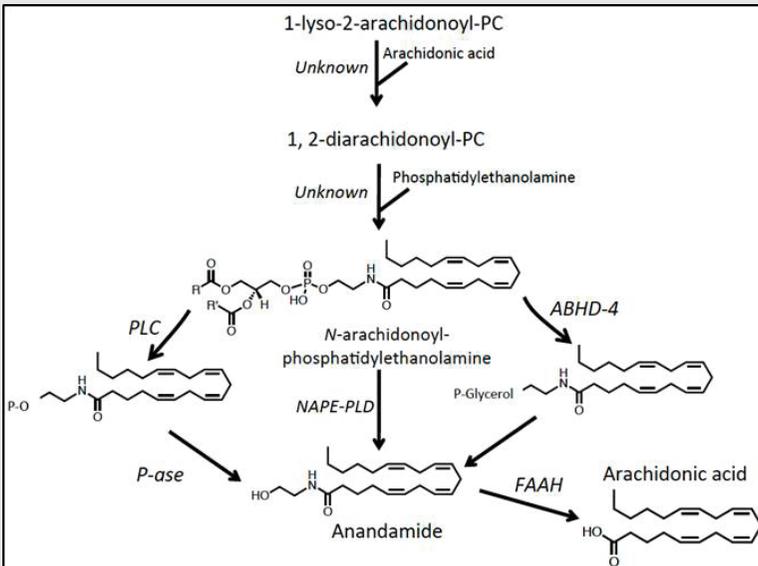


FIGURE 2-3 Pathways of anandamide formation and deactivation.

Endocannabinoid Synaptic Signaling (CB₁) (A Central Example)

One of the best-studied forms of endocannabinoid signaling occurs at CNS synapses. There are several unique features of endocannabinoid signaling relative to amino acid and peptide-based neurotransmitters. First, endocannabinoid signaling occurs in a retrograde direction, i.e., the signaling is initiated in postsynaptic neurons and acts upon presynaptic terminals. This is in stark contrast to traditional

continued

BOX 2-1 Continued

anterograde chemical neurotransmission, which is initiated at the axon terminal and conveys signals to postsynaptic neurons within a connected neuronal circuit or system. A second unique feature of this system is that, in contrast to classical neurotransmitters, endocannabinoids are not preformed and stored in vesicles pending release. In contrast, they are produced “on demand” upon stimulation of postsynaptic cells through a variety of signals.

The role of 2-AG in mediating endocannabinoid synaptic signaling has been well established during the past decade. Indeed, at excitatory synapses, all key components of 2-AG-mediated signaling (DGL- α , MGL, CB₁ receptor) are ideally localized to facilitate retrograde control of neurotransmitter release. Specifically, DGL- α is found in postsynaptic spines while MGL and CB₁ are located in axon terminals. The activity of DGL- α can be increased by stimulation of Gq-coupled-neurotransmitter receptors (e.g., metabotropic glutamate receptors) or by a calcium influx. Once active, DGL- α generates 2-AG at the cell membrane, which travels in a retrograde direction to the presynaptic terminal to interact with CB₁. The activation of CB₁ by 2-AG results in a reduction in presynaptic release probability predominantly via Gi/o-dependent signal transduction cascades. This synaptic depression can last for seconds to minutes or longer, depending on the duration of receptor stimulation and the specific types of downstream signaling cascades initiated. After interacting with the receptor, 2-AG is hydrolyzed primarily by MGL located in the cytosol of the presynaptic axon terminal. MGL in astrocytes may also contribute to the termination of 2-AG-mediated synaptic signaling.

There is also evidence that anandamide can act as a retrograde modulator of neurotransmitter release in a manner similar to 2-AG, but with some distinct differences that are suggestive of a broader paracrine mode of action.

SOURCE: Piomelli, 2015.

CANNABIS-DERIVED PRODUCTS

In the United States, cannabis-derived products are consumed for both medical and recreational purposes in a variety of ways. These include smoking or inhaling from cigarettes (joints), pipes (bowls), water pipes (bongs, hookahs), and blunts (cigars filled with cannabis); eating or drinking food products and beverages; or vaporizing the product. These different modes are used to consume different cannabis products, including cannabis “buds” (dried cannabis flowers); cannabis resin (hashish, bubble hash); and cannabis oil (butane honey oil, shatter, wax, crumble). The oil, which may contain up to 75 percent Δ^9 -THC—versus 5 to 20 percent in the herb or resin (Raber et al., 2015)—is extracted from plant material using organic solvents, such as ethanol, hexane, butane, or supercritical

(or subcritical) CO₂, and can be either smoked or vaporized by pressing the extracted oil against the heated surface of an oil rig pipe (dabbing). Cannabinoids can also be absorbed through the skin and mucosal tissues, so topical creams, patches, vaginal sprays, and rectal suppositories are sometimes employed and used as a form of administering Δ⁹-THC (Brenneisen et al., 1996). A broad selection of cannabis-derived products are also available in the form of food and snack items, beverages, clothing, and health and beauty aid products.

Potency of Cannabis

In the 1990s and early 2000s, the bulk of cannabis consumed in the United States was grown abroad and illicitly imported. The past decade has seen an influx of high-potency cannabis produced within the United States—for example, “sinsemilla”—which is grown from clones rather than from seeds. Data from the U.S. Drug Enforcement Administration (DEA) seizures record a substantial increase in average potency, from 4 percent in 1995 to roughly 12 percent in 2014, both because high-quality U.S.-grown cannabis has taken market share from Mexican imports and because cannabis from both sources has grown in potency (ElSohly et al., 2016; Kilmer, 2014).

Route of Administration

The route of administration of cannabis can affect the onset, intensity, and duration of the psychotropic effects, the effects on organ systems, and the addictive potential and negative consequences associated with its use (Ehrler et al., 2015). The consumption of cannabis causes a particular combination of relaxation and euphoria, commonly referred to as a “high.” When cannabis is smoked, Δ⁹-THC quickly diffuses to the brain, eliciting a perceived high within seconds to minutes. Blood levels of Δ⁹-THC reach a maximum after about 30 minutes and then rapidly subside within 1 to 3.5 hours (Fabritius et al., 2013; Huestis et al., 1992). Vaping has an onset, peak, and duration that are similar to those of smoking and produces a similar high (Abrams et al., 2007). “Dabbing,” a term for flash-vaporizing butane hash oil-based concentrates, has been reported to offer a different and stronger intoxicating effect than smoking/vaping (Loflin and Earleywine, 2014). By contrast, eating does not produce effects for 30 minutes to 2 hours, and the perceived high is relatively prolonged, lasting 5 to 8 hours or even longer. The slow action of orally ingested cannabis is due to Δ⁹-THC being absorbed by the intestine and transported to the liver (hepatic first pass) where it is converted into 11-OH-THC, an equipotent and longer-lasting metabolite (Huestis et al., 1992). Edibles make

it harder to titrate the intoxicating effects due to the delayed and variable onset. Consequently, edibles have been tied to the ingestion of excessive amounts of cannabis under the misperception that the initial dose had not produced the desired effect (Ghosh and Basu, 2015; MacCoun and Mello, 2015). The availability of edibles has also been associated with increased rates of accidental pediatric ingestion of cannabis (Wang et al., 2014).

Trends in Routes of Administration

There are no high-quality nationally representative data on the prevalence of the non-herbal forms of cannabis (e.g., edibles, oils, and other concentrates), but evidence suggests that they are more commonly used by medical cannabis patients in states with recreational or lenient medical cannabis policies (Daniulaityte et al., 2015; Pacula et al., 2016). Forty percent of 12th-grade past-year users reported using cannabis in edible form in medical cannabis states, versus 26 percent in states without medical cannabis laws (NIDA, 2014). In Washington State, an online survey from 2013 found that, among daily and near-daily cannabis users, 27.5 percent had used edibles, 22.8 percent had used hash resin, and 20.4 percent had “dabbed” in the past week (Kilmer et al., 2013).

Data from recreational cannabis sales in Washington and Colorado provide a glimpse of trends that are specific to markets that have legalized cannabis. In Washington State, herbal cannabis remains dominant, having accounted for two-thirds of all sales revenues in June 2016, but it is losing market share as “cannabis extracts for inhalation” become more popular, at 21 percent in June 2016 as compared with 12 percent 1 year prior. The sales of liquid and solid edibles (9 percent) combined account for most of the remaining sales.⁴ Non-herbal varieties are even more popular on Colorado’s recreational market, where herbal cannabis accounts for a narrow majority (56 percent) and sales of solid concentrates (24 percent) and edibles (13 percent) are on the rise (Castle, 2016).

Partly to provide a guide for the responsible use of non-herbal varieties of cannabis, states that have legalized the recreational cannabis have defined a standard “dose” of THC. Washington State and Colorado have set the standard “dose” of THC as 10 mg, while Oregon chose a lower limit of 5 mg. For perspective, the typical joint size in the United States is 0.66 g (Mariani et al., 2011) and the average potency is 8 percent THC (Fabritius et al., 2013), resulting in an average dose of 8.25 mg THC per joint; higher THC levels ranging from 15–20 percent or higher would yield

⁴ Author’s calculations from Washington State Liquor and Cannabis Board’s publicly available August 2016 “traceability” dataset (“biotrackthc_dispersing.csv”). Data requests available at: <http://lcb.wa.gov/records/public-records> (accessed January 5, 2017).

a THC dose between 9.9–13.2 mg. Occasional users report feeling “high” after consuming only 2–3 mg of THC (Hall and Pacula, 2010); however, users who have developed tolerance to the effects of THC via frequent use may prefer much larger quantities.

CLINICAL FEATURES OF CANNABIS INTOXICATION

During acute cannabis intoxication, the user’s sociability and sensitivity to certain stimuli (e.g., colors, music) may be enhanced, the perception of time is altered, and the appetite for sweet and fatty foods is heightened. Some users report feeling relaxed or experiencing a pleasurable “rush” or “buzz” after smoking cannabis (Agrawal et al., 2014). These subjective effects are often associated with decreased short-term memory, dry mouth, and impaired perception and motor skills. When very high blood levels of Δ^9 -THC are attained, the person may experience panic attacks, paranoid thoughts, and hallucinations (Li et al., 2014). Furthermore, as legalized medical and recreational cannabis availability increase nationwide, the impairment of driving abilities during acute intoxication has become a public safety issue.

In addition to Δ^9 -THC dosage, two main factors influence the intensity and duration of acute intoxication: individual differences in the rate of absorption and metabolism of Δ^9 -THC, and the loss of sensitivity to its pharmacological actions. Prolonged CB₁ receptor occupation as a consequence of the sustained use of cannabis can trigger a process of desensitization, rendering subjects tolerant to the central and peripheral effects of Δ^9 -THC and other cannabinoid agonists (Gonzalez et al., 2005). Animals exposed repeatedly to Δ^9 -THC display decreased CB₁ receptor levels as well as impaired coupling between CB₁ and its transducing G-proteins (Gonzalez et al., 2005). Similarly, in humans, imaging studies have shown that chronic cannabis use leads to a down-regulation of CB₁ receptors in the cortical regions of the brain and that this effect can be reversed by abstinence (Hirvonen et al., 2012).

CANNABINOID-BASED MEDICATIONS

The U.S. Food and Drug Administration (FDA) has licensed three drugs based on cannabinoids (see Table 2-2). Dronabinol, the generic name for synthetic Δ^9 -THC, is marketed under the trade name of Marinol[®] and is clinically indicated to counteract the nausea and vomiting associated with chemotherapy and to stimulate appetite in AIDS patients affected by wasting syndrome. A synthetic analog of Δ^9 -THC, nabilone (Cesamet[®]), is prescribed for similar indications. Both dronabinol and nabilone are given orally and have a slow onset of action. In July 2016 the

TABLE 2-2 Cannabinoid-Based Medications

CANNABINOID-BASED MEDICATIONS			
	Substance	Route of Administration	Description
Natural Product Derived Compounds	Cannabidiol (CBD)	Oral capsule Oromucosal spray	Cannabinoid extracted from <i>Cannabis</i> plant
	Cannabis	Multiple	Multiple active cannabinoids
	Cannador	Oral capsule	THC and CBD from <i>Cannabis</i> extract
	Epidiolex® (FDA Fast Track)	Oil	Concentrated CBD from <i>Cannabis</i> extract
	Nabiximol (Sativex®) (FDA Fast Track)	Oromucosal spray	THC and CBD extract from two <i>Cannabis</i> plant varieties
	Tetrahydrocannabinol (THC)	Oral capsule Smoked Oromucosal spray	Active cannabinoid of <i>Cannabis</i> plant
	THC/CBD	Oral capsule	Combination of cannabinoids
Synthetic Compounds	Ajulemic acid (AjA) (FDA PHASE II Active)	Oral capsule	Synthetic nonpsychoactive cannabinoid
	Dronabinol (Marinol®; Syndros®) (FDA approved)	Oral capsule	Synthetic THC
	Nabilone (Cesamet®) (FDA approved)	Oral capsule	Synthetic cannabinoid—THC analogue

FDA approved Syndros®, a liquid formulation of dronabinol, for the treatment of patients experiencing chemotherapy-induced nausea and vomiting who have not responded to conventional antiemetic therapies. The agent is also indicated for treating anorexia associated with weight loss in patients with AIDS. Two additional cannabinoid-based medications have been examined by the FDA. Nabiximols (Sativex®) is an ethanol cannabis extract composed of Δ^9 -THC and CBD in a one-to-one ratio. Nabiximols is administered as an oromucosal spray and is indicated in the symptomatic relief of multiple sclerosis and as an adjunctive analgesic treatment in cancer patients (Pertwee, 2012). As of September 2016, nabiximols has

been launched in 15 countries, including Canada, Germany, Italy, Spain, the United Kingdom, and has been approved in a further 12, but not in the United States.⁵ In response to the urgent need expressed by parents of children with intractable epilepsy, in 2013 the FDA allowed investigational new drug studies of Epidiolex[®], a concentrated CBD oil (>98 percent CBD), also developed by GW Pharmaceuticals, as an anti-seizure medication for Dravet and Lennox-Gastaut syndromes.

SYNTHETIC CANNABINOIDS AS RECREATIONAL DRUGS

In addition to nabilone, many other synthetic cannabinoids agonists have been described and widely tested on experimental animals to investigate the consequences of cannabinoid receptor activation⁶ (e.g., CP-55940, WIN-55212-2, JWH-018) (Iversen, 2000; Pertwee, 2012). The therapeutic application of these highly potent molecules is limited by their CB₁-mediated psychotropic side effects, which presumably provide the rationale for the illicit use of some of them as an alternative to cannabis (Wells and Ott, 2011). Preclinical and clinical data in support of this claim remain very limited, however. Internet-marketed products such as Spice, K2, and Eclipse are a blend of various types of plant material (typically herbs and spices) that have been sprayed with one of these synthetic cannabinoids (as well as other non-cannabinoid psychoactive drugs). Since 2009 more than 140 different synthetic cannabinoids have been identified in herbal mixtures consumed as recreational drugs. The synthetic cannabinoids used in “herbal mixtures” are chemically heterogeneous, most of them being aminoalkylindole derivatives such as naphthoylindoles (e.g., JWH-018 and JWH-210), cyclopropylindoles (e.g., UR-144, XLR-11), or quinoline esters (e.g., PB-22). They seem to appeal especially to young cannabis and polydrug users because they are relatively inexpensive, easily available through the Internet, and difficult to identify with standard immunoassay drug screenings. In contrast to Δ⁹-THC, which is a partial agonist of the CB₁ receptor, many of the synthetic cannabinoids bind to CB₁ receptors with high affinity and efficacy, which may also be associated with higher potential of toxicity (Hermanns-Clausen et al., 2016). According to the National Institute on Drug Abuse (NIDA, 2012, p. 2), people using these various blends have been admitted to Poison Control Centers reporting “rapid heart rate, vomiting, agitation, confusion, and hallucinations.” Synthetic cannabinoids can also raise blood pressure and cause a reduced blood supply to the heart (myocardial ischemia), and in a

⁵ For additional information see: <http://www.gwpharm.com> (accessed January 5, 2017).

⁶ Due to the determined scope of this report, nontherapeutic synthetic cannabinoids will not be discussed in the forthcoming chapters of the report.

few cases they have been associated with heart attacks. Regular users may experience withdrawal and symptoms of dependence (Tait et al., 2016).

CANNABIS CONTAMINANTS AND ADULTERANTS

The large economic potential and illicit aspect of cannabis has given rise to numerous potentially hazardous natural contaminants or artificial adulterants being reported in crude cannabis and cannabis preparations. Most frequent natural contaminants consist of degradation products, microbial contamination (e.g., fungi, bacteria), and heavy metals. These contaminants are usually introduced during cultivation and storage (McLaren et al., 2008). Growth enhancers and pest control chemicals are the most common risks to both the producer and the consumer. Cannabis can also be contaminated for marketing purposes. This usually entails adding substances (e.g., tiny glass beads, lead) to increase the weight of the cannabis product (Busse et al., 2008; Randerson, 2007) or adding psychotropic substances (e.g., tobacco, calamus) and cholinergic compounds to either enhance the efficacy of low-quality cannabis or to alleviate its side effects (McPartland et al., 2008). Additionally, some extraction and inhalation methods used for certain dosing formulations (tinctures, butane hash oil, “dabs”) can result in substantial pesticide and solvent contamination (Thomas and Pollard, 2016).

REFERENCES

- Abrams, D. I., H. P. Vizoso, S. B. Shade, C. Jay, M. E. Kelly, and N. L. Benowitz. 2007. Vaporization as a smokeless cannabis delivery system: A pilot study. *Clinical Pharmacology and Therapeutics* 82(5):572–578.
- Adams, R., M. Hunt, and J. H. Clark. 1940a. Structure of cannabidiol, a product isolated from the marihuana extract of Minnesota wild hemp. I. *Journal of the American Chemical Society* 62(1):196–200.
- Adams, R., D. C. Pease, C. K. Cain, B. R. Baker, J. H. Clark, H. Wolff, and R. B. Wearn. 1940b. Conversion of cannabidiol to a product with marihuana activity. *Journal of the American Chemical Society* 62(8):2245–2246.
- Agrawal, A., P. A. Madden, K. K. Bucholz, A. C. Heath, and M. T. Lynskey. 2014. Initial reactions to tobacco and cannabis smoking: A twin study. *Addiction* 109(4):663–671.
- American Herbal Pharmacopoeia. 2013. *Cannabis inflorescence: Cannabis spp.: Standards of identity, analysis, and quality control*. Scott’s Valley, CA: American Herbal Pharmacopoeia.
- Bergamaschi, M. M., R. H. Queiroz, M. H. Chagas, D. C. de Oliveira, B. S. De Martinis, F. Kapczinski, J. Quevedo, R. Roesler, N. Schröder, A. E. Nardi, R. Martín-Santos, J. E. Hallak, A. W. Zuardi, and J. A. Crippa. 2011. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. *Neuropsychopharmacology* 36(6):1219–1226.
- Bisogno, T., L. Hanus, L. De Petrocellis, S. Tchilibon, D. E. Ponde, I. Brandi, A. S. Moriello, J. B. Davis, R. Mechoulam, and V. Di Marzo. 2001. Molecular targets for cannabidiol and its synthetic analogues: Effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *British Journal of Pharmacology* 134(4):845–852.

- Brenneisen, R., A. Egli, M. A. Elsohly, V. Henn, and Y. Spiess. 1996. The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: A pilot study with 2 patients. *International Journal of Clinical Pharmacology and Therapeutics* 34(10):446–452.
- Busse, F., L. Omid, K. Timper, A. Leichtle, M. Windgassen, E. Kluge, and M. Stumvoll. 2008. Lead poisoning due to adulterated marijuana. *New England Journal of Medicine* 358(15):1641–1642.
- Carrier, E. J., J. A. Auchampach, and C. J. Hillard. 2006. Inhibition of an equilibrative nucleoside transporter by cannabidiol: A mechanism of cannabinoid immunosuppression. *Proceedings of the National Academy of Sciences of the United States of America* 103(20):7895–7900.
- Castle, S. 2016. More growers brings surge in weed supplies, plunge in Boulder County pot prices. *Daily Camera*, August 26. http://www.dailycamera.com/boulder-business/ci_30295353/bumper-crop-growers-leads-surge-weed-supplies-plunge (accessed November 8, 2016).
- Chandra, S., H. Lata, I. A. Khan, M. A. ElSohly. 2013. The role of biotechnology in *Cannabis sativa* propagation for the production of phytocannabinoid. In S. Chandra, H. Lata, I. A. Khan, and M. A. ElSohly (eds.), *Biotechnology for medicinal plants*. Berlin: Springer-Verlag. Pp. 123–148.
- Clarke, R. C., and M. D. Merlin. 2015. *Cannabis: Evolution and ethnobotany*. Berkeley: University of California Press.
- Daniulaityte, R., R. W. Nahhas, S. Wijeratne, R. G. Carlson, F. R. Lamy, S. S. Martins, E. W. Boyer, G. A. Smith, and A. Sheth. 2015. Time for dabs: Analyzing Twitter data on marijuana concentrates across the U.S. *Drug and Alcohol Dependence* 155:307–311.
- de Lago, E. and J. Fernandez-Ruiz. 2007. Cannabinoids and neuroprotection in motor-related disorders. *CNS and Neurological Disorders in Drug Targets* 6(6):377–387.
- De Petrocellis, L., A. Ligresti, A. S. Moriello, M. Allarà, T. Bisogno, S. Petrosino, C. G. Stott, and V. Di Marzo. 2011. Effects of cannabinoids and cannabinoid-enriched cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. *British Journal of Pharmacology* 163(7):1479–1494.
- Devane, W. A., F. A. Dysarz, 3rd, M. R. Johnson, L. S. Melvin, and A. C. Howlett. 1988. Determination and characterization of a cannabinoid receptor in rat brain. *Molecular Pharmacology* 34(5):605–613.
- Ehrler, M. R., E. C. Deborah, and D. A. Yurgelun-Todd. 2015. Subjective and cognitive effects of cannabinoids in marijuana smokers. In P. Campolongo and L. Fattore (eds.), *Cannabinoid modulation of emotion, memory, and motivation*. New York: Springer. Pp. 159–181.
- Elmes, M. W., M. Kaczocha, W. T. Berger, K. Leung, B. P. Ralph, L. Wang, J. M. Sweeney, J. T. Miyauchi, S. E. Tsirka, I. Ojima, and D. G. Deutsch. 2015. Fatty acid-binding proteins (FABPs) are intracellular carriers for Delta9-tetrahydrocannabinol (THC) and cannabidiol (CBD). *Journal of Biological Chemistry* 290(14):8711–8721.
- ElSohly, M. A., and W. Gul. 2014. *Constituents of cannabis sativa*. In *Handbook of Cannabis*. Oxford, UK: Oxford University Press. P. 20.
- ElSohly, M. A., Z. Mehmedic, S. Foster, C. Gon, S. Chandra, and J. C. Church. 2016. Changes in cannabis potency over the last 2 decades (1995–2014): Analysis of current data in the United States. *Biological Psychiatry* 79(7):613–619.
- Fabritius, M., H. Chtioui, G. Battistella, J. M. Annoni, K. Dao, B. Favrat, E. Fornari, E. Lauer, P. Maeder, and C. Giroud. 2013. Comparison of cannabinoid concentrations in oral fluid and whole blood between occasional and regular cannabis smokers prior to and after smoking a cannabis joint. *Analytical and Bioanalytical Chemistry* 405(30):9791–9803.
- Galal, A. M., D. Slade, W. Gul, A. T. El-Alfy, D. Ferreira, and M. A. Elsohly. 2009. Naturally occurring and related synthetic cannabinoids and their potential therapeutic applications. *Recent Patents on CNS Drug Discovery* 4:112–136.

- Gaoni, Y., and R. Mechoulam. 1964. Isolation, structure, and partial synthesis of an active constituent of hashish. *Journal of the American Chemical Society* 86(8):1646–1647.
- Ghosh, A., and D. Basu. 2015. Cannabis and psychopathology: The meandering journey of the last decade. *Indian Journal of Psychiatry* 57(2):140–149.
- Gonzalez, S., M. Cebeira, and J. Fernández-Ruiz. 2005. Cannabinoid tolerance and dependence: A review of studies in laboratory animals. *Pharmacology Biochemistry and Behavior* 81(2):300–318.
- Grotenhermen, F. 2003. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clinical Pharmacokinetics* 42(4):327–360.
- Hall, W. D., and R. L. Pacula. 2010. *Cannabis use and dependence: Public health and public policy*. (reissue of 2003 first edition). Cambridge, UK: Cambridge University Press.
- Herkenham, M., A. B. Lynn, M. D. Little, M. R. Johnson, L. S. Melvin, B. R. de Costa, and K. C. Rice. 1990. Cannabinoid receptor localization in brain. *Proceedings of the National Academy of Sciences of the United States* 87(5):1932–1936.
- Hermanns-Clausen, M., J. Kithinji, M. Spehl, V. Angerer, F. Franz, F. Eyer, and V. Auwärter. 2016. Adverse effects after the use of JWH-210—A case series from the EU Spice II plus project. *Drug Testing and Analysis* 8(10):1030–1038.
- Hillig, K. W. 2005. Genetic evidence for speciation in Cannabis (Cannabaceae). *Genetic Resources and Crop Evolution* 52(2):161–180.
- Hirvonen, J., R. S. Goodwin, C. T. Li, G. E. Terry, S. S. Zoghbi, C. Morse, V. W. Pike, N. D. Volkow, M. A. Huestis, and R. B. Innis. 2012. Reversible and regionally selective down-regulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. *Molecular Psychiatry* 17(6):642–649.
- Hofmann, M. E., and C. J. Frazier. 2013. Marijuana, endocannabinoids, and epilepsy: Potential and challenges for improved therapeutic intervention. *Experimental Neurology* 244:43–50.
- Huestis, M. A., J. E. Henningfield, and E. J. Cone. 1992. Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. *Journal of Analytical Toxicology* 16(5):276–282.
- IOM (Institute of Medicine). 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC: National Academy Press.
- Iuvone, T., G. Esposito, D. De Filippis, C. Scuderi, and L. Steardo. 2009. Cannabidiol: A promising drug for neurodegenerative disorders? *CNS Neuroscience and Therapeutics* 15(1):65–75.
- Iversen, L. 2000. *The science of marijuana*. New York: Oxford University Press.
- Jones, N. A., A. J. Hill, I. Smith, S. A. Bevan, C. M. Williams, B. J. Whalley, and G. J. Stephens. 2010. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. *Journal of Pharmacology and Experimental Therapeutics* 332(2):569–577.
- Kilmer, B. 2014. Policy designs for cannabis legalization: Starting with the eight Ps. *The American Journal of Drug and Alcohol Abuse* 40(4):259–261.
- Kilmer, B., J. P. Caulkins, G. Midgette, L. Dahlkemper, R. J. MacCoun, and R. L. Pacula. 2013. *Before the grand opening: Measuring Washington State's marijuana market in the last year before legalized commercial sales*. Santa Monica, CA: RAND Corporation.
- Kuddus, M., I. A. M. Ginawi, and A. Al-Hazimi. 2013. Cannabis sativa: An ancient wild edible plant of India. *Emirates Journal of Food and Agriculture* 25(10):736–745.
- Lakhan, S. E., and M. Rowland. 2009. Whole plant cannabis extracts in the treatment of spasticity in multiple sclerosis: A systematic review. *BMC Neurology* 9:59.
- Laprairie, R. B., A. M. Bagher, M. E. Kelly, and E. M. Denovan-Wright. 2015. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. *British Journal of Pharmacology* 172(20):4790–4805.
- Laursen, L. 2015. Botany: The cultivation of weed. *Nature* 525(7570):S4–S5.

- Leweke, F. M., J. K. Mueller, B. Lange, and C. Rohleder. 2016. Therapeutic potential of cannabinoids in psychosis. *Biological Psychiatry* 79(7):604–612.
- Li, R. F., G. T. Lu, L. Li, H. Z. Su, G. F. Feng, Y. Chen, Y. Q. He, B. L. Jiang, D. J. Tang, and J. L. Tang. 2014. Identification of a putative cognate sensor kinase for the two-component response regulator HrpG, a key regulator controlling the expression of the *hrp* genes in *Xanthomonas campestris* pv. *campestris*. *Environmental Microbiology* 16(7):2053–2071.
- Loflin, M., and M. Earleywine. 2014. A new method of cannabis ingestion: The dangers of dabs? *Addictive Behaviors* 39(10):1430–1433.
- Long, T., M. Wagner, D. Demske, C. Leipe, and P. E. Tarasov. 2016. Cannabis in Eurasia: Origin of human use and Bronze Age trans-continental connections. *Vegetation History and Archaeobotany* 25:1–14.
- MacCoun, R. J., and M. M. Mello. 2015. Half-baked—The retail promotion of marijuana edibles. *New England Journal of Medicine* 372(11):989–991.
- Mackie, K. 2006. Cannabinoid receptors as therapeutic targets. *Annual Review of Pharmacology and Toxicology* 46:101–122.
- Mariani, J. J., D. Brooks, M. Haney, and F. R. Levin. 2011. Quantification and comparison of marijuana smoking practices: Blunts, joints, and pipes. *Drug and Alcohol Dependence* 113(2-3):249–251.
- Matsuda, L. A., S. J. Lolait, M. J. Brownstein, A. C. Young, and T. I. Bonner. 1990. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* 346(6284):561–564.
- McLaren, J., W. Swift, P. Dillon, and S. Allsop. 2008. Cannabis potency and contamination: A review of the literature. *Addiction* 103(7):1100–1109.
- McPartland, J. M., D. J. Blanchon, and R. E. Musty. 2008. Cannabimimetic effects modulated by cholinergic compounds. *Addiction Biology* 13(3-4):411–415.
- Mechoulam, R., and Y. Shvo. 1963. Hashish. I. The structure of cannabidiol. *Tetrahedron* 19(12):2073–2078.
- Moreau de Tours, J. J. 1845. *Du Hachisch et de L'alienation mentale*. Paris: Librairie de Fortin, Masson et Ca.
- Munro, S., K. L. Thomas, and M. Abu-Shaar. 1993. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 365(6441):61–65.
- NIDA (National Institute on Drug Abuse). 2012. *DrugFacts: Spice (Synthetic Marijuana)*. Rockville, MD: U.S. Department of Health and Human Services, National Institutes of Health.
- NIDA. 2014. *Monitoring the Future Survey, Overview of Findings 2014*. <https://www.drugabuse.gov/related-topics/trends-statistics/monitoring-future/monitoring-future-survey-overview-findings-2014> (accessed November 14, 2016).
- O'Shaughnessy, W. B. 1840. New remedy for tetanus and other convulsive disorders. *The Boston Medical and Surgical Journal* 23:153–155.
- Pacula, R. L., M. Jacobson, and E. J. Maksabedian. 2016. In the weeds: A baseline view of cannabis use among legalizing states and their neighbours. *Addiction* 111(6):973–980.
- Pertwee, R. G. 2012. Targeting the endocannabinoid system with cannabinoid receptor agonists: Pharmacological strategies and therapeutic possibilities. *Philosophical Transactions of the Royal Society of London B: Biological Sciences* 367(1607):3353–3363.
- Piomelli, D. 2015. *Neurobiology of marijuana*. In *Textbook of Substance Abuse Treatment*, M. Galanter, H. D. Kleber, and K. T. Brady, eds. Arlington VA: American Psychiatric Publishing. Pp. 335–350.
- Raber, J. C., S. Elzinga, and C. Kaplan. 2015. Understanding dabs: Contamination concerns of cannabis concentrates and cannabinoid transfer during the act of dabbing. *Journal of Toxicological Science* 40(6):797–803.

- Randerson, J. 2007. Warning issued over cannabis adulterated with glass beads. *The Guardian*, January 12. <https://www.theguardian.com/society/2007/jan/12/drugsandalcohol.drugs> (accessed November 8, 2016).
- Russo, E. B. 2007. History of cannabis and its preparations in saga, science, and sobriquet. *Chemistry and Biodiversity* 4(8):1614–1648.
- Russo, E. B., A. Burnett, B. Hall, and K. K. Parker. 2005. Agonistic properties of cannabidiol at 5-HT_{1a} receptors. *Neurochemical Research* 30(8):1037–1043.
- Scuderi, C., D. D. Filippis, T. Iuvone, A. Blasio, A. Steardo, and G. Esposito. 2009. Cannabidiol in medicine: A review of its therapeutic potential in CNS disorders. *Phytotherapy Research* 23(5):597–602.
- Small, E. 2015. Evolution and classification of *Cannabis sativa* (marijuana, hemp) in relation to human utilization. *The Botanical Review* 81(3):189–294.
- Tait, R. J., D. Caldicott, D. Mountain, S. L. Hill, and S. Lenton. 2016. A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. *Clinical Toxicology* 54(1):1–13.
- Thomas, A., G. L. Baillie, A. M. Phillips, R. K. Razdan, R. A. Ross, and R. G. Pertwee. 2007. Cannabidiol displays unexpectedly high potency as an antagonist of CB₁ and CB₂ receptor agonists in vitro. *British Journal of Pharmacology* 150(5):613–623.
- Thomas, B. F., and G. T. Pollard. 2016. Preparation and distribution of cannabis and cannabis-derived dosage formulations for investigational and therapeutic use in the United States. *Frontiers in Pharmacology* 7:285.
- U.S. Pharmacopoeial Convention. 1916. *Pharmacopoeia of the United States*. Philadelphia, PA: P. Blakiston's Son & Company.
- Wang, G. S., G. Roosevelt, M. C. Le Lait, E. M. Martinez, B. Bucher-Bartelson, A. C. Bronstein, and K. Heard. 2014. Association of unintentional pediatric exposures with decriminalization of marijuana in the United States. *Annals of Emerging Medicine* 63(6):684–689.
- Wells, D. L. and C. A. Ott. 2011. The new marijuana. *Annals of Pharmacotherapy* 45(3):414–417.
- Wollner, H. J., J. R. Matchett, J. Levine, and S. Loewe. 1942. Isolation of a physiologically active tetrahydrocannabinol from *Cannabis sativa* resin. *Journal of the American Chemical Society* 64(1):26–29.

3

Cannabis: Prevalence of Use, Regulation, and Current Policy Landscape

PREVALENCE OF CANNABIS USE IN THE UNITED STATES (1975–2014)

The popularity of cannabis has ebbed and flowed over the past century. Despite being outlawed in several states in the early 1900s and being federally prohibited in 1937, cannabis remained relatively obscure until the 1960s, when an upsurge in use among adolescents and young adults brought the drug into the mainstream. Since the early 1970s, two surveys, the National Survey on Drug Use and Health (NSDUH) and Monitoring the Future, have provided nationally representative data on self-reported use of cannabis. The NSDUH (called the National Household Survey on Drug Abuse until 2002) has polled Americans 12 years of age and older since 1971, and Monitoring the Future has polled high school seniors since 1976, adding 8th- and 10th-graders in 1991 (CBHSQ, 2014; ICPSR, 2016). Both national surveys include questions that ask respondents whether they have ever used cannabis and if they have used cannabis within the past year or within the past 30 days. These data have been used to categorize users, with those reporting use within the past month often considered to be “active” or “current” users. Monitoring the Future also asks youth about how easily they could access cannabis, whether they approve of its use, and how risky they perceive it to be. Other national surveys of interest include the Centers for Disease Control and Prevention’s (CDC’s) Youth Risk Behavior Survey, which surveys the health-risk behaviors of

9th- through 12th-grade students on a biannual basis,¹ and the CDC's Behavioral Risk Factor Surveillance System,² which collects state and local data regarding health-related risk behaviors, chronic health conditions, and the use of preventive services. It is of note that many surveillance surveys differ in their design and methodology, which often limits the ability to compare and compile data across studies.

The prevalence of cannabis use peaked in the late 1970s, when more than one-third of high school seniors (37 percent in 1976) and one in eight Americans over 12 years old (12.8 percent in 1979) reported past-month use (Johnston et al., 2016). Self-reported past-month use declined throughout the 1980s and by 1992 was just one-third of the 1970s peak, both among high school seniors (12.1 percent) and the general population (4.4 percent). The recorded decline in use did not last long. The mid-1990s saw rapid increases, with use by high school seniors nearly doubling within just the 5 years from 1992 (11.9 percent) to 1997 (23.7 percent). Throughout the late 1990s and early 2000s, the rates of use largely stagnated, with trends among youth and the general population moving roughly in parallel (Johnston et al., 2016).

The years since 2007 have seen steady year-over-year increases in general population past-month use, rising from 5.8 percent to 8.4 percent in 2014 (a 45 percent increase). There is no single clear explanation for the post-2007 increases in use. Hypothesized causes include declining potency-adjusted prices on the illicit market; the proliferation of medical cannabis laws, especially those that allow for sale at brick-and-mortar dispensaries; and changing public perceptions about the harms of cannabis use (Sevigny et al., 2014).

Today, cannabis is the most popular illicit drug in the United States (in terms of past-month users), trailed by prescription-type drugs used for nonmedical purposes, such as pain relievers (3.8 million), tranquilizers (1.9m), and stimulants (1.7m), and by prohibited drugs such as cocaine (1.9m), hallucinogens (1.2m), and heroin (0.3m) (CBHSQ, 2016a). A recent survey showed that the primary use of cannabis in the United States remains recreational (89.5 percent of adult cannabis users), with only 10.5 percent reporting use solely for medical purposes, and 36.1 percent reporting a mixed medical/recreational use (Schauer et al., 2016).

In 2015, an estimated 22.2 million of more than 265 million Americans 12 years of age or older reported having used cannabis in the past month (8.3 percent) (CBHSQ, 2016a). Cannabis use is most prevalent among

¹ For additional information see: <http://www.cdc.gov/healthyouth/data/yrbs/results.htm> (accessed January 6, 2017).

² For additional information see: <http://www.cdc.gov/brfss/about/index.htm> (accessed January 6, 2017).

young people ages 18 to 25 (19.8 percent using in the past month) (CBHSQ, 2016a). Interestingly, since 2002 the use of cannabis has decreased among 12- to 17-year-olds, while it has markedly increased in the senior population, that is, those over 55 years (Azofeifa et al., 2016).

Males are nearly twice as likely (10.6 percent) to use cannabis as females (6.2 percent) (see Table 3-1). Black Americans use cannabis at the highest rate among major ethnic groups (10.7 percent), followed by whites (8.4 percent) and Hispanics (7.2 percent) (CBHSQ, 2016b). Use is also more common among lower-income Americans and those without college degrees (Davenport and Caulkins, 2016).

Different demographics have different rates of cannabis use. For example, dividing the population by age yields stark differences. Data from the Monitoring the Future survey show that more than one-fifth (21.3 percent) of high school seniors reported past-month use in 2015

TABLE 3-1 Past-Month Use Rates by Demographic

	Past-Month Use Rate (%)
Ethnicity	
White, Non-Hispanic	8.4
African American, Non-Hispanic	10.7
Hispanic	7.2
Asian Non-Hispanic	3.0
Gender	
Male	10.6
Female	6.2
Education	
Less Than High School	8.2
High School Graduate	9.1
Some College	10.5
College Grad	5.9
Family Income^a	
Less than \$10k	13.6
\$20k–\$29.9k	9.7
\$50k–\$74.9k	7.8
\$75k +	6.6
Age^a	
12–17	7.1
18–25	20.1
26–34	13.0
35–49	7.1
50+	3.9

^a Calculated with the Substance Abuse and Mental Health Services Administration's (SAMHSA's) public online data analysis system (PDAS). Crosstab: IRMJRC × CATAG3 (CBHSQ, 2016b).

SOURCE: Derived from CBHSQ, 2016b.

(Johnston et al., 2016). According to NSDUH data, past-month use is highest among 18- to 25-year-olds (19.8 percent) and lower in older groups. All age groups have shown increases in past-month cannabis use since 2002, with the sole exception of adolescents between ages 12 and 17, whose use in 2015 (7.0 percent) was lower than that reported in 2002 (8.2 percent) (CBHSQ, 2016a).

Volume and Intensity of Cannabis Use Today

A different and often overlooked picture of cannabis use is painted when it is measured in terms of volume or intensity of use rather than the prevalence of current users. The NSDUH survey asks past-month cannabis users how many days in the past 30 they have used “marijuana or hashish,” allowing researchers to measure the volume of use by aggregating reported use-days or by tracking the number of users who report use on more than 20 days in the past 30, termed heavy or “daily/near-daily” users.

Today, 22.2 million Americans 12 years of age and older report current cannabis use (defined as “users in the past 30 days”) (CBHSQ, 2016a). As a proportion of past-month users, heavy users have grown from roughly one in nine in 1992 to more than one in three (35.4 percent) in 2014, indicating an increased intensity of use among current users.³ Furthermore, the population of heavy users has not only become larger, it has also become older. Burns et al. note an inversion of the ratio of youth (ages 12–17) to older adults (ages 50 and older): in 2002, more than three times as many youths as older adults were using cannabis on a daily or near-daily basis; by 2011, 2.5 times as many adults as youth were daily or near-daily cannabis users (Burns et al., 2013).

Generally, the intensity of use correlates with use prevalence: groups with high prevalence tend to be the same as those with high intensity. But some groups are noticeable exceptions. For example, Americans with less than a high school education are less likely to report past-month use than Americans with a high school diploma or with a partial college education, but in terms of past-month use, those with less than a high school education are most likely to report daily/near-daily use (44.8 percent). Likewise, among age demographics, 26- to 34-year-olds report less past-month use than 18- to 25-year-olds do, but they report substantially more

³ Computed by NSDUH cross-tabs for 1992 and 2014. For 1992: <https://www.icpsr.umich.edu/icpsrweb/ICPSR/series/64/studies/6887?archive=ICPSR&sortBy=7> (accessed January 6, 2017). Compute “MRJMON” against “MJDAY30A,” recoded as “MJDAY30A(r: 0-20;21-30).” For 2014: <http://www.icpsr.umich.edu/cgi-bin/SDA/NAHDAP/hsda?nahdap+36361-0001> (accessed January 6, 2017). Compute “IRMJRC” against “MJDAY30A,” recoded as “MJDAY30A(r: 0-20;21-30).”

heavy use among current users (42.2 percent). Heavy use among past-month users is lowest among 12- to 17-year-olds (7.4 percent). Younger users tend to have lighter habits. According to Monitoring the Future data, in 2015, 6 percent of high school seniors who used cannabis in the past month reported use on a *daily* basis, as did 3 percent of 10th-graders and 1.1 percent of 8th-graders (Johnston et al., 2016).

One result of the increased intensity of use among past-month users is that the bulk of cannabis consumption is increasingly concentrated among a small number of heavy users. By one estimate, the one-third of current cannabis users that use daily or near daily accounted for two-thirds of the reported days of past-month use and three-quarters of expenditures (Davenport and Caulkins, 2016).

CANNABIS REGULATION IN THE UNITED STATES

In the United States at the turn of the 20th century, cannabis was generally used for medical rather than recreational purposes. As such, the production and use of cannabis was regulated by consumer safety laws such as the Pure Food and Drug Act of 1906, which required producers to disclose and label the quantity of cannabis present in any product sold as food or medicine. Although several U.S. states enacted bans on cannabis between 1911 and 1930, it escaped early federal prohibitions, such as the Harrison Act of 1914, which regulated opium and derivatives of the coca plant (Musto, 1999).

Fear of “marihuana,” as cannabis was beginning to be called, grew during the 1920s and 1930s as immigration from Mexico steadily increased in southwestern states. In the mid-1930s, the federal government, through the Federal Bureau of Narcotics, endorsed state-level actions and encouraged states to adopt the Marihuana Tax Act as a means to criminalize the unregistered and untaxed production and use of cannabis. National prohibition did not take shape, however, until Congress passed the Marihuana Tax Act of 1937, which regulated the production, distribution, and use of cannabis via Congress’s power to tax commerce. The act required those dealing with cannabis to register with federal authorities and pay a tax (Booth, 2005; Musto, 1999). The supply and use of the drug was not criminalized, but nonmedical supply or use was a violation and subject to a fine and imprisonment.

Today, cannabis is regulated by local, state, federal, and international law. State laws often mirror federal law, enshrined in the Comprehensive Drug Abuse Prevention and Control Act of 1970, which includes the Controlled Substances Act (CSA). The CSA modernized and consolidated earlier federal drug laws, making them consistent with international drug control conventions, specifically the United Nations Single Convention

on Narcotic Drugs of 1961, which the United States ratified (Caulkins et al., 2016). The CSA placed cannabis in Schedule I, the most restrictive category reserved for substances that have no currently accepted medical use, alongside heroin and lysergic acid diethylamide (LSD). The federal government does not recognize the medical use of cannabis, citing no evidence of the accepted medical use of herbal cannabis. It bears mentioning that pharmaceutical-grade cannabinoids have been isolated and are scheduled apart from cannabis. For example, tetrahydrocannabinol (THC) is sold as Marinol[®], available with prescription (a Schedule III drug). That THC, which is the principal active ingredient in cannabis, in its pure form is listed in Schedule III indicates that the placement of botanical or whole cannabis in Schedule 1 may be driven by the lack of recognition of medical use for the whole plant.

Federal criminal law prohibits the supply and use of cannabis with exceptions for medical and scientific purposes. The enforcement of cannabis prohibition by federal authorities has focused on international smuggling and domestic crop eradication as well as violations on federal lands. The federal government has relied on state and local authorities to enforce criminal prohibitions on cannabis retail and use. In 2014 there were more than 1.5 million arrests for drug law violations,⁴ approximately 30,000 of which were made by the U.S. Drug Enforcement Administration (DEA).⁵ However, federal law remains an important factor in regulating cannabis. While the National Institutes of Health (NIH) have funded cannabis research—\$111 million on 281 cannabinoid research projects in 2015 alone (NIH, 2016)—the federal government has restricted research on cannabis by licensing a single producer under contract with the National Institute on Drug Abuse (NIDA) and requiring multiple administrative reviews on research proposals (Caulkins et al., 2016) (see Chapter 15—Challenges and Barriers in Conducting Cannabis Research for additional information).⁶ Federal law also prohibits the importation of and intra- and interstate trade in cannabis. Tangentially, federal banking and commercial laws impede the development of commercial cannabis businesses. Though

⁴ As a noteworthy caveat, within the United States there is evidence of racial, social, and economic status-based disparities in the enforcement and issued penalties related to cannabis sale and use (Austin and Ressler, 2016). Within this context, it is important to acknowledge the potential impact of these laws on the health outcomes of disenfranchised communities.

⁵ See <https://ucr.fbi.gov/crime-in-the-u.s/2014/crime-in-the-u.s.-2014/tables/table-29> (accessed January 6, 2017) and <https://www.dea.gov/resource-center/statistics.shtml#arrests> (accessed January 6, 2017).

⁶ In August 2016, NIDA announced a policy change intended to support an increase in the number of DEA-registered marijuana manufacturers. This change was designed to ensure a larger and more diverse supply of marijuana for U.S. Food and Drug Administration (FDA)-authorized research purposes (DEA, 2016).

legal at the state level, the federal prohibition on cannabis prevents businesses from accessing the banking sector, precluding entrepreneurs from accessing lines of credit, electronic funds transfer, checking accounts, and other financial goods and services available to contemporary businesses. Federal tax code also prohibits cannabis businesses from deducting typical costs of business (Caulkins et al., 2015; Oglesby, 2015). In summary, the legal changes in cannabis policy during the past 50 years have been characterized primarily by three types of policies, each implemented by various states, beginning with (1) decriminalization throughout the 1970s, which preceded (2) medical cannabis laws and (3) regulated and licensed recreational cannabis.

Decriminalization of Possession and Use

States and localities perform most of the legwork involved in enforcing the criminal prohibition on cannabis as they arrest and convict the vast majority of offenders. Each state maintains its own set of laws that regulate the supply and use of the drug. In most cases, acts involving cannabis are subject to criminal prohibition, but sanctions vary considerably by state, each of which is constitutionally entitled to establish its own criminal codes and penalties.

The reduction of statutory penalties for use-related acts, including personal possession, is referred to as *decriminalization* or *depenalization*. About a dozen U.S. states are often described as having decriminalized possession in the 1970s (Pacula et al., 2005), beginning with Oregon in 1973. This move to reduce penalties on cannabis use halted until 2001 when Nevada decriminalized possession of small amounts of cannabis. Today, 21 states and the District of Columbia have decriminalized possession of small amounts of cannabis (Caulkins et al., 2016).

During the 1970s, the federal government briefly considered abolishing criminal sanctions for use-related acts. The 1972 National Commission on Marihuana and Drug Abuse, appointed by President Nixon, recommended that federal law be amended to decriminalize cannabis possession, use, and low-level retail (Shafer Commission, 1972). Those recommendations were rejected by the Nixon administration. President Carter raised the issue again in a 1977 speech to Congress, calling for federal decriminalization of cannabis possession, but his administration did not succeed in changing policies (Musto, 1999).

Medical Cannabis Laws

The next major shift in state cannabis policy in the United States was the enactment of medical cannabis laws. Starting in 1996 California

passed a popular referendum (Proposition 215) to allow individuals suffering from various illnesses to use herbal, whole plant cannabis, making California the first jurisdiction in the Western Hemisphere to legalize medical cannabis in some form. The law generally provides an affirmative defense for individuals using cannabis for medical purposes. Reforms at the state level continued in the waning years of the 20th century, with a handful of states passing laws to allow doctors to prescribe medical cannabis or allow for a legal defense for use of medical cannabis. The permission of use of the flower or products derived from the cannabis flower has now spread to 28 states and the District of Columbia. Another 16 states allow limited access to low-tetrahydrocannabinol (THC)/high-cannabidiol (CBD) products (NCSL, 2016). Figure 3-1 demonstrates that low-THC/high-CBD laws are a recent phenomenon.

Medical cannabis laws and policies vary greatly in terms of the regulations governing supply and use. Some are more restrictive than others, limiting the access of the drug to a certain class of individuals who suffer from certain illnesses or conditions, or establishing stricter limits on the production and distribution of the substance to at-home cultivation by patients and caregivers. Some states legally protect and regulate the

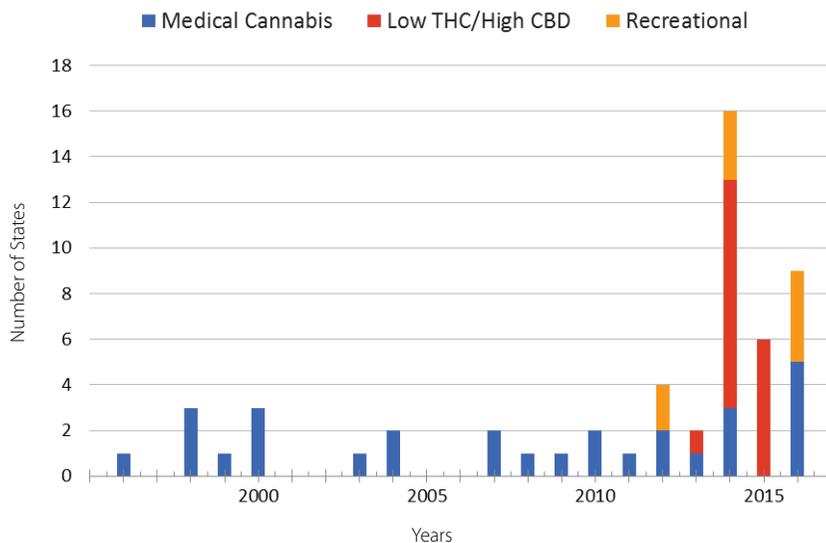


FIGURE 3-1 Passage of state cannabis laws (figure includes the District of Columbia).

SOURCE: Adapted from NCSL, 2016.

operation of storefronts known as dispensaries. In these states, patients with a recommendation can enter stores and obtain a wide array of cannabis and cannabis products. Some dispensaries openly advertise their wares and services to patients at point of sale, with others aggressively promoting their business to the general public.

When it comes to the distribution of medical cannabis, some states, such as New York, restrict the sale of medical cannabis to non-smokable forms of the drug. Others require that patients register with the state and identify their source of cannabis. Even within states regulations may vary. Some states allow for local bans and municipal ordinances to help regulate additional aspects of the supply of cannabis.

Nonmedical, Adult Recreational Use

In 2010 California voted on legalizing recreational cannabis—in effect, permitting and regulating the supply and distribution of cannabis for adults to use nonmedically. Proposition 19 sought to repeal the state’s criminal prohibitions on cannabis, regulating it for recreational purposes for those over 21 years of age. The initiative failed, with 54 percent voting against. Two years later residents of Colorado, Oregon, and Washington went to the polls to vote on legalizing the adult recreational use of cannabis. Oregon’s initiative failed, with 53 percent of voters rejecting the measure⁷; however, Colorado and Washington State, after passing ballot initiatives in November 2012, became the first jurisdictions to legalize the large-scale commercial production of cannabis for recreational use for adults over 21, with Colorado also permitting home cultivation. In November 2014 similar initiatives were approved by voters in Alaska⁸ and Oregon. The District of Columbia took a narrower approach by legalizing only possession and home cultivation. The DC City Council subsequently attempted to permit and regulate a commercial market but was blocked by the U.S. Congress.

The liberalization of cannabis laws has been a gradual process. Early steps included medical cannabis, including the allowance and, sometimes, legal protection of dispensaries. Later, Alaska, Colorado, Oregon, and Washington State regulated the production and distribution of recreational cannabis by private, for-profit commercial actors along similar lines. Besides the general commercial design of these initiatives, the details of the regulations vary. Table 3-2 describes a few of the regula-

⁷ Oregon temporarily allowed sales of recreational cannabis through existing medical dispensaries beginning in October 2015, though licensed recreational stores are not expected to open until late 2016.

⁸ Alaska is expected to allow recreational cannabis sales in licensed stores by late 2016.

tory differences between Alaska, Colorado, Oregon, Washington, and the District of Columbia. With the exception of Washington State, all permit at-home cultivation. The District of Columbia follows a “grow and give” noncommercial model. None impose potency limits or require users to register.

In November 2016, California, Maine, Massachusetts, and Nevada voted to legalize adult measures related to recreational cannabis use

TABLE 3-2 Regulatory Differences Across Four States and the District of Columbia That Have Legalized Recreational Cannabis

	Alaska	Colorado
Legal Process	Voter initiative, state statute	Voter initiative, amendment to state constitution
When Passed	November 2014	November 2012
When Implemented	February 2015: Personal possession, consumption, cultivation Late 2016 (expected): Retail sales	December 2012: Personal possession, consumption, cultivation January 2014: Retail sales
Regulatory Authority	Marijuana Control Board (Alcoholic Beverage Control Board)	Marijuana Enforcement Division (Department of Revenue)
Minimum Age	21	21
Residency Requirement	None	None
Personal Possession Quantity	28.5 g	28.5 g
Home Cultivation	6 plants, 3 of which can be flowering	6 plants, 3 of which can be flowering
Interpersonal Sharing	28.5 g	28.5 g
Retail Transaction Limit	28.5 g	Residents: 28.5 g Non-residents: 7 g
Retail Pricing Structure	Market	Market
Average Retail Price per Gram After Tax	No retail stores currently	\$11.50
Maximum THC Content	None	None

and possession (NORML, 2016). Arkansas, Florida, Montana, and North Dakota voted in favor of medical marijuana initiatives. In order to develop and enforce regulations for a recreational cannabis industry, each state has appointed a regulatory agency. Alaska, Oregon, and Washington State delegated this responsibility to existing alcohol authorities, while Colorado expanded the responsibilities of the Medical Marijuana Enforcement Division under the Department of Revenue. To aid in drafting rules fol-

Oregon	Washington	District of Columbia
Voter initiative, state statute	Voter initiative, state statute	Voter initiative
November 2014	November 2012	November 2014
July 2015: Personal possession, consumption, cultivation October 1, 2015: Retail sales via medical dispensaries Late-2016 (expected): retail sales through licensed retailers	December 2012: Personal possession, consumption July 2014: Retail sales	February 2015: Personal possession, consumption, cultivation
Oregon Liquor Control Commission	Liquor and Cannabis Board (formerly the Liquor Control Board)	Not applicable
21	21	21
None	None	None
In public: 28.5 g At home: 228 g	28.5 g	57 g
4 plants in flower	Not allowed	6 plants per person 12 plants per household, 3 of which can be flowering
28.5 g	Not allowed	28.5 g
7 g	28.5 g	Not applicable
Market	Market	Not applicable
\$10.00	\$10.00	Not applicable
None	None	None

continued

TABLE 3-2 Continued

	Alaska	Colorado
Registration Requirements	None	None
Advertising	Final advertising regulations to be determined by the Alaska Department of Health and Social Services Division of Public Health	Restricted to media with no more than 30 percent of the audience under the age of 21
Taxation	\$50 excise tax per ounce on sales or transfers from cultivation facility to retail store or product manufacturer	15 percent excise tax on cultivation; 10 percent retail marijuana sales tax; 2.9 percent state sales tax; local sales taxes
Cannabis Clubs	Not explicitly allowed or prohibited; ban on in-store consumption repealed in November 2015	Not allowed
Medical Cannabis	2000: Patient registry, possession, home cultivation	2000: Patient registry, possession, consumption 2010: Commercial production and sales

SOURCE: Adapted from UNODC World Drug Report 2016 (UNODC, 2016).

lowing the passage of their initiatives, state agencies held public hearings and working groups to solicit public input (Pardo, 2014).

The federal government has not challenged these state laws by invoking the supremacy clause of the U.S. Constitution. However, under the 10th Amendment, as reaffirmed by U.S. jurisprudence, the federal government cannot force a state to criminalize an act under state law (Garvey and Yeh, 2014). When the voters of these states passed initiatives to legalize, regulate, and tax recreational cannabis, they simultaneously repealed the penal provisions and sanctions prohibiting and criminalizing unauthorized cultivation, trafficking, and possession of cannabis. Under the Obama administration, the federal government seems to have opted for a more pragmatic solution which allows for a rules-based cannabis industry, as dictated by state regulations, while maintaining the future option to preempt.

Oregon	Washington	District of Columbia
None	None	None
Entry sign required on exterior of dispensaries; Oregon Liquor Control Commission has authority to further regulate or prohibit advertising	Limited to one sign for retailers at business location	Not applicable, no commercial market
October–December 2015: No tax on retail sales; after January 5, 2016: 25 percent sales tax	July–June 2014: 25 percent tax at each stage (production, processing, retail) July 2015: 37 percent sales tax	Not applicable, no commercial market
Not allowed	Not allowed	Not allowed; currently under investigation by city task force.
1999: Patient registry, possession, home cultivation	1999: Possession 2012: Home cultivation, no patient registry	2011: Patient registry

POLICY LANDSCAPE

Most researchers recognize that a growing general public acceptance of the drug for medical and recreational purposes has been encouraging the changes at the state level. It remains to be seen if cannabis will be legalized at the national level or if such public opinion will continue. In 2015, according to a Gallup tracker poll, 58 percent of Americans favored legalizing cannabis, marking the third straight year that cannabis legalization found majority support (Gallup, 2015). Given that a large percentage of the U.S. population lives in states that permit some degree of access to THC-containing compounds via either the medical or the recreational market, it is important to examine the current policy landscape, which may shape future state and federal regulations of cannabis.

State-Level Changes

State-Regulated Use

Cannabis policy change has occurred at the state level in large part due to changing public sentiment. Many states have reformed their cannabis laws, not from a deliberative legislative process but through popular referendums. As discussed earlier, states have passed laws to allow qualifying individual's access to medical cannabis. These laws can be broadly divided into three distinct categories: loose medical, restricted access, and non-THC.

Some of the earliest laws passed—and the laws generally found in most states west of the Mississippi River—are referred to as *loose medical*. In states with these policies, access to medical cannabis is not strictly limited to provable qualifying ailments, such as terminal cancer, HIV/AIDS, or glaucoma. A patient may access medical cannabis when his or her physician deems it necessary, and in some jurisdictions this amounts to little more than de facto legalization of recreational use. One study that surveyed more than 4,000 individuals seeking access to medical cannabis in California concluded that the typical patient was a white male in his early 30s who started using cannabis in his teens with fewer reported disabilities than the national average (O'Connell and Bou-Matar, 2007). Under *restricted access*, patients must meet certain qualifying criteria (such as a qualifying medical condition) or are restricted to what types of medical products are available, or both. For example, New York prohibits the use of smokable herbal cannabis, allowing only tinctures, oils, concentrates, and other forms of products. *Non-THC* laws permit the use of no-THC or low-THC/high-CBD products, such as CBD oil, to treat a short list of qualifying conditions, such as refractory epilepsy. This category is by far the most restrictive, and states that adopt these non-THC policies generally prohibit the supply and distribution of such products, granting only a legal defense for their use.

That said, 28 states and the District of Columbia fall in one or the other of the first two categories and allow for loose or restricted medical use, where patients may access some form of THC-containing compound. Sixteen states fall in the non-THC category. A total of 44 states and the District of Columbia have amended their laws to allow for some form of medical cannabis (NCSL, 2016) (see Figure 3-2).

Of all the jurisdictions that allow for some sort of access to THC-containing compounds, cancer, HIV/AIDS, multiple sclerosis, and glaucoma are among the most recognized qualifying ailments (NCSL, 2016). And examination of all jurisdictions shows that most list seizures and epileptic seizures within their statutes (NCSL, 2016). However, several states are open in their interpretation, allowing for medical cannabis to

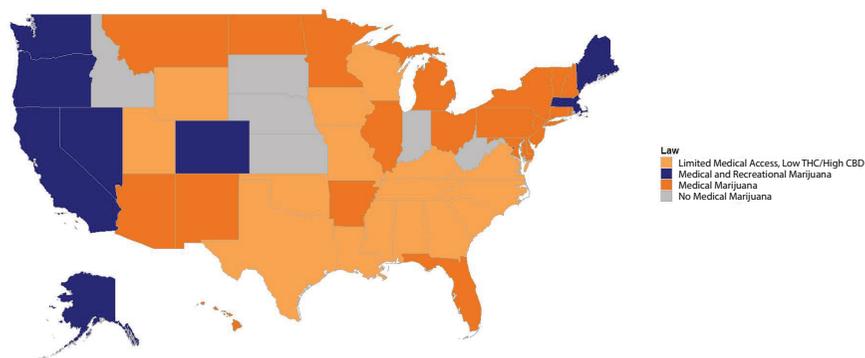


FIGURE 3-2 Cannabis laws by state, November 2016.

SOURCE: Adapted from NCSL, 2016.

be used to treat any illness for which the drug provides relief. Since few states maintain medical cannabis patient registries, the committee relied on data on the percentage of patients reporting certain qualifying illnesses in Oregon and Colorado (see Figure 3-3). As can be seen in the figure, the overwhelming majority obtained a recommendation on the basis of a claimed need to treat pain.

State Research on Therapeutic Effects

In addition to state-level legal changes that regulate cannabis for either medical or recreational purposes, a few states have sought to expand research into cannabis's therapeutic effects. The Center for Medicinal Cannabis Research (CMCR) at the University of California was created in 2000 to conduct clinical and preclinical studies of cannabinoids, including smoked cannabis, for conditions for which cannabis may be beneficial. With state funding, the CMCR approved 21 federally approved studies: 13 have been completed, and 6 have been discontinued (CMCR, 2016).

Departing from this, Colorado has started to conduct research into the medicinal value of cannabis that is neither federally funded nor federally approved. In 2014 Colorado passed legislation to promote research into cannabis's medical benefits, creating the Medical Marijuana Scientific Advisory Council and appropriating \$9 million in research grants. The advisory council approves research grants and evaluates research. As of early 2015, nine research grants have been approved, with six studies cur-

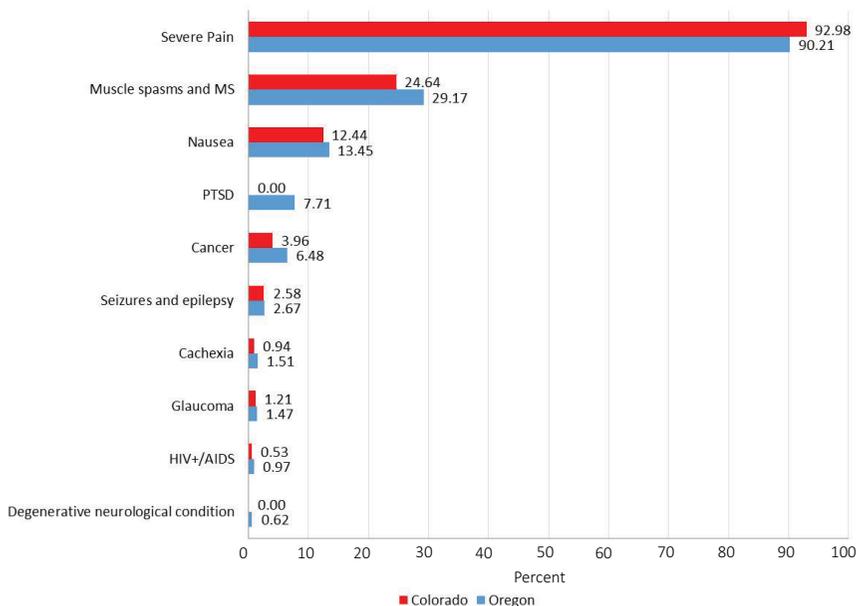


FIGURE 3-3 Percentage of medical cannabis patients reported by condition in Colorado and Oregon, July 2016.

NOTE: Patients may report multiple qualifying ailments.

SOURCES: Adapted from CDPHE, 2016; OHA, 2016.

rently under way.⁹ Also in 2015, NIH provided \$111 million in funding for 281 cannabinoid-related research efforts nationwide (NIH, 2016).

EXECUTIVE BRANCH POLICIES

Federal Regulated Use

As discussed earlier, the executive branch of the federal government has extensive influence and impact when it comes to regulating cannabis. Despite the complex domestic arrangements established by the U.S. Constitution and the current political climate, the executive branch has not challenged state-level laws that are in violation with federal drug laws. The Obama administration has issued a series of federal guidelines for

⁹ See the Colorado Department of Public Health and Environment's Medical Marijuana Scientific Advisory Council: <https://www.colorado.gov/pacific/cdphe/approved-medical-marijuana-research-grants> (accessed January 6, 2017).

states that are reforming cannabis laws, granting limited space for such policies.

In 2009 the U.S. Department of Justice issued a policy memo declaring that it was not the federal government's intent to prosecute individuals who abide by state medical cannabis laws (Ogden, 2009). That policy was later updated in August 2013 following the legalization of nonmedical cannabis in Colorado and Washington State. The current policy guidelines outline eight enforcement criteria whereby the federal government may intervene and prosecute an individual or group for violating the Controlled Substances Act (Cole, 2013). Furthermore, the U.S. Department of Justice stated that it expects states that have legalized cannabis to implement robust systems of enforcement and regulation to protect public health and safety; however, recent evaluations of the policy guidelines suggest that the U.S. Department of Justice has done little to evaluate how states comply with federal priorities (GAO, 2016).

Because cannabis is still federally prohibited, laws that govern other aspects of commerce—namely, banking and finance—have prevented businesses that deal in cannabis from accessing lines of credit or banking (McErlean, 2015). Money laundering laws and the CSA prevent many banks from interacting with cannabis businesses. In order to ease this conflict, the U.S. Department of the Treasury, through the Financial Crimes Enforcement Network (FinCEN), has issued a directive to financial establishments allowing them to deal with cannabis businesses that comply with state laws (FinCEN, 2014).

Federal Research

Despite ongoing federal funding for cannabinoid research (\$111 million in 2015 alone), cannabis researchers have found federal research funds to be restricted and limited. Research proposals were required to undergo a thorough and rigorous assessment by the DEA, NIDA, the FDA, and the U.S. Department of Health and Human Services (HHS). If they were federally approved, researchers were limited in the type and quantity of cannabis available from the University of Mississippi, which was contracted by NIDA to act as the only licit supply of the drug for research. (See Chapter 15—Challenges and Barriers in Conducting Cannabis Research for additional information.) In 2015 the Obama administration, via HHS and the DEA, relaxed some regulatory restrictions, eliminating duplicative reviews of research proposals by the HHS as well as increasing the amount of cannabis available for research by raising the aggregate production quota of cannabis cultivated at the University of Mississippi (DEA, 2016).

In August 2016 the DEA denied a petition to reschedule cannabis to

Schedule II, citing that cannabis has no currently accepted medical use in treatment in the United States (DEA, 2016). The administration did, however, adopt a new policy to end the NIDA-contracted monopoly of research-grade cannabis by the University of Mississippi. Under new rules, the DEA will facilitate cannabis research by increasing the number of private entities allowed to cultivate and distribute research-grade cannabis (DEA, 2016).

CONGRESSIONAL BRANCH POLICIES

Recently the 113th Congress used its regulatory powers to shape cannabis policy at both the state and the subnational level. In the Consolidated and Further Continuing Appropriations Act of 2015 (Public Law No. 113-235), lawmakers precluded the U.S. Department of Justice from using fiscal year 2015 appropriated funds to enforce the Controlled Substances Act to prevent states from implementing their own laws that authorize the use, distribution, possession, or cultivation of medical cannabis (Sec 538). In the same piece of legislation, Congress precluded the District of Columbia from using appropriated funds to regulate, legalize, or otherwise reduce penalties for the possession, distribution, or use of any Schedule I substance, effectively blocking any citywide effort to regulate the trade in cannabis (Sec 908b). During the same session, Congress authorized the Secretary of Agriculture to promulgate rules to ensure that medical cannabis costs are not treated as a deduction in Supplemental Nutrition Assistance Program (SNAP) benefits as well as allowing universities and state departments of agriculture to cultivate industrial hemp for research purposes (Garvey et al., 2015).

Members of the current 114th Congress have proposed several pieces of legislation on cannabis. Some would remove cannabis from the Controlled Substances Act and treat the drug like alcohol. Others would end the civil asset forfeiture of real property of businesses that comply with state medical cannabis laws or authorize the U.S. Department of Veterans Affairs to offer recommendations regarding veterans' use of cannabis in compliance with state regimes. One bill in particular, the Medical Marijuana Research Act, has gained bipartisan support from proponents and opponents of cannabis reform in Congress. The bill would increase cannabis research by making the drug and plant more accessible to researchers.

PUBLIC OPINION

Public opinion toward cannabis seems to be driving many of the policy changes that have taken place to date. Cannabis found mainstream market appeal in the late 1960s and early 1970s, and, as a result, polling

agencies started surveying the public opinion about the drug. In 1969 the Gallup Poll began asking Americans if they thought that the “use of cannabis should be made legal,” and the company has continued to ask Americans the same question for nearly 50 years.¹⁰

Gallup poll responses showed that support for legal cannabis use increased to 28 percent in 1977 (the same year President Carter called for national decriminalization). For about 20 years, support declined and then plateaued at around 24 percent, only to inch upward 4 years after California passed legislation in favor of medical cannabis. By 2000, 31 percent of respondents favored legal use. Over the past 6 years support has vacillated, but it averaged 48 percent from 2010 through 2012 and has averaged 56 percent since 2013. In 2015, 58 percent of respondents favored legal use.

Polling shows that the public is overwhelmingly in favor of the use of cannabis for medical purposes if prescribed by a doctor. No other company has tracked public opinion concerning medical cannabis over time in the same way as the Gallup Poll, but a collection of national surveys from ProCon indicate that since 1998, 60 to 85 percent of Americans have been supportive of the use of medical cannabis (ProCon, 2016). In a recent poll by Quinnipiac, 89 percent of respondents supported medical cannabis (Quinnipiac, 2016). However, it is of note that states attribute different medicinal value to different forms of the drug, restricting who can access what part of the plant. National surveys may not capture these distinctions that are made in state-level law or policy. Yet, the general shift over time suggests that the public is welcoming some changes in cannabis policy and law. There appears to be greater agreement that cannabis should be available as a medicine to those with certain qualifying conditions, but it is harder to find similar political agreement on recreational cannabis. It is unclear whether the wording of the Gallup Poll’s public opinion question paints an accurate picture of the current and ongoing sentiment with respect to states that are legalizing recreational cannabis.

POLICY AND RESEARCH

The political landscape for the commercialization, decriminalization, and use of cannabis is constantly evolving. As federal and state agencies continue to grapple with these important public policy issues, it is important to consider that each political decision may have significant public health implications.

¹⁰ It should be noted that the question is somewhat vague, implying “legalization” but referring to “use” of cannabis, not the legal production and distribution of the drug. This ambiguity may cloud respondents’ answers.

As laws and policies continue to change, research must also. Unfortunately, research on the health effects and potential therapeutic potential of cannabis use has been limited in this country, despite enormous changes at the state level. As such, there is currently limited research evidence to guide policy. This lack of aggregated knowledge is a significant impediment not only to the scientific understanding of cannabis but also to the advancement of public policy and the nation's overall public health.

REFERENCES

- Austin, W., and R. W. Ressler. 2016. Who gets arrested for marijuana use? The perils of being poor and black. *Applied Economics Letters* [Epub May 4, 2016], 1–3.
- Azofeifa, A., M. E. Mattson, G. Schauer, T. McAfee, A. Grant, and R. Lyerla. 2016. National estimates of marijuana use and related indicators—National Survey on Drug Use and Health, United States, 2002–2014. *Morbidity and Mortality Weekly Report* 65(SS-11):1–25.
- Booth, M. 2005. *Cannabis: A history*. New York: St. Martin's Press (Macmillan Publishers).
- Burns, R. M., J. P. Caulkins, S. S. Everingham, and B. Kilmer. 2013. Statistics on cannabis users skew perceptions of cannabis use. *Front Psychiatry* 4:138.
- Caulkins, J. P., B. Kilmer, M. Kleiman, R. J. MacCoun, G. Midgette, P. Oglesby, R. L. Pacula, and P. H. Reuter. 2015. *Considering marijuana legalization*. http://www.rand.org/content/dam/rand/pubs/research_reports/RR800/RR864/RAND_RR864.pdf (accessed November 22, 2016).
- Caulkins, J. P., B. Kilmer, A. Hawken, and M. Kleiman. 2016. *Marijuana legalization: What everyone needs to know*. New York: Oxford University Press.
- CBHSQ (Center for Behavioral Health Statistics and Quality). 2014. *National Survey on Drug Use and Health (NSDUH): Summary of methodological studies, 1971–2014*. Rockville, MD: Substance Abuse and Mental Health Services Administration.
- CBHSQ. 2016a. *Key substance use and mental health indicators in the United States: Results from the 2015 National Survey on Drug Use and Health*. Rockville, MD: Substance Abuse and Mental Health Services Administration. <https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2015/NSDUH-FFR1-2015/NSDUH-FFR1-2015.pdf> (accessed January 9, 2017).
- CBHSQ. 2016b. *2015 National Survey on Drug Use and Health: Detailed tables*. Rockville, MD: Substance Abuse and Mental Health Services Administration. <https://www.samhsa.gov/data/sites/default/files/NSDUH-DefTabs-2015/NSDUH-DefTabs-2015/NSDUH-DefTabs-2015.pdf> (accessed December 27, 2016).
- CDPHE (Colorado Department of Public Health and Environment). 2016. *Medical Marijuana Registry Program statistics, July 31, 2016*. https://www.colorado.gov/pacific/sites/default/files/CHED_MMR_Monthly_Report_Statistics_July_2016.pdf (accessed October 12, 2016).
- CMCR (Center for Medical Cannabis Research). 2016. Research: Active studies, pending studies, completed studies, discontinued studies. <http://www.cmcrc.ucsd.edu> (accessed December 16, 2016).
- Cole, J. M. 2013. *Memorandum for all United States attorneys*. August 29. <https://www.justice.gov/iso/opa/resources/3052013829132756857467.pdf> (accessed November 10, 2016).
- Davenport, S., and J. P. Caulkins. 2016. Evolution of the United States marijuana market in the decade of liberalization before full legalization. *Journal of Drug Issues* 46(4):411–427.
- DEA (U.S. Drug Enforcement Administration). 2016. *DEA announces actions related to marijuana and industrial hemp*. <https://www.dea.gov/divisions/hq/2016/hq081116.shtml> (accessed November 10, 2016).

- FinCEN (Financial Crimes Enforcement Network). 2014. *BSA expectations regarding marijuana-related businesses*. February 14. <https://www.fincen.gov/sites/default/files/shared/FIN-2014-G001.pdf> (accessed November 10, 2016).
- Gallup (Gallup Tracking Poll). 2015. *In U.S., 58% back legal marijuana use*. <http://www.gallup.com/poll/186260/back-legal-marijuana.aspx> (accessed December 17, 2016).
- GAO (U.S. Government Accountability Office). 2016. *State marijuana legalization: DOJ should document its approach to monitoring the effects of legalization*. February 1. GAO-16-1. <http://www.gao.gov/products/GAO-16-1> (accessed November 10, 2016).
- Garvey, T., and B. T. Yeh. 2014. *State legalization of recreational marijuana: Selected legal issues*. Congressional Research Service, January 13. <https://fas.org/sgp/crs/misc/R43034.pdf> (accessed November 10, 2016).
- Garvey, T., C. Doyle, and D. H. Carpenter. 2015. *Marijuana: Medical and retail—Selected legal issues*. Congressional Research Service. April 8. <https://fas.org/sgp/crs/misc/R43435.pdf> (accessed November 10, 2016).
- ICPSR (Interuniversity Consortium for Political and Social Research). 2016. *Monitoring the Future (MTF) Series*. <https://www.icpsr.umich.edu/icpsrweb/ICPSR/series/35> (accessed January 9, 2017).
- Johnston, L. D., P. M. O'Malley, R. A. Miech, J. G. Bachman, and J. E. Schulenberg. 2016. *Monitoring the Future: National survey results on drug use, 1975–2015: Overview: key findings on adolescent drug use*. Ann Arbor: Institute for Social Research, University of Michigan.
- McErlean, E. D. 2015. The real green issue regarding recreational marijuana: Federal tax and banking laws in need of reform. *DePaul Law Review* 64(4):1079–1118.
- Musto, D. F. 1999. *The American disease: Origins of narcotic control*. New York: Oxford University Press.
- NCSL (National Conference of State Legislatures). 2016. *State medical marijuana laws*. November 9. <http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx> (accessed November 10, 2016).
- NIH (National Institutes of Health). 2016. *NIH research on marijuana and cannabinoids*. <https://www.drugabuse.gov/drugs-abuse/marijuana/nih-research-marijuana-cannabinoids> (accessed December 16, 2016).
- NORML. 2016. *Election 2016—Marijuana Ballot Results*. <http://norml.org/election-2016> (accessed December 22, 2016).
- O'Connell, T. J., and C. B. Bou-Matar. 2007. Long term marijuana users seeking medical cannabis in California (2001–2007): Demographics, social characteristics, patterns of cannabis and other drug use of 4,117 applicants. *Harm Reduction Journal* 4(1):16.
- Ogden, D. 2009. Memorandum for selected United States attorneys on investigations and prosecutions in states authorizing the medical use of marijuana. October 19. <https://www.justice.gov/opa/blog/memorandum-selected-united-state-attorneys-investigations-and-prosecutions-states> (accessed November 10, 2016).
- Oglesby, P. 2015. *Supplemental thoughts about revenue from marijuana in Vermont* (January 16, 2015). <https://ssrn.com/abstract=2551029> or <http://dx.doi.org/10.2139/ssrn.2551029> (accessed December 16, 2016).
- OHA (Oregon Health Authority). 2016. *Oregon Medical Marijuana Program Statistical Snapshot July, 2016*. <https://public.health.oregon.gov/DiseasesConditions/ChronicDisease/MedicalMarijuanaProgram/Documents/OMMP-Statistical-Snapshot%20-07-2016.pdf> (accessed October 12, 2016).
- Pacula, R. L., R. MacCoun, P. Reuter, J. Chriqui, B. Kilmer, K. Harris, L. Paoli, and C. Schäfer. 2005. What does it mean to decriminalize marijuana? A cross-national empirical examination. *Advances in Health Economics and Health Services Research* 16:347–369.
- Pardo, B. 2014. Cannabis policy reforms in the Americas: A comparative analysis of Colorado, Washington, and Uruguay. *International Journal of Drug Policy* 25(4):727–735.

- ProCon (ProCon.org). 2016. *Votes and polls, national*. <http://medicalmarijuana.procon.org/view.additional-resource.php?resourceID=000151> (accessed December 10, 2016).
- Quinnipiac (Quinnipiac University Poll). 2016. *Allow marijuana for vets with PTSD, U.S. voters say 10-1, Quinnipiac University national poll finds; slim majority says legalize marijuana in general*. <https://poll.qu.edu/national/release-detail?ReleaseID=2354> (accessed December 16, 2016).
- Schauer, G. L., B. A. King, R. E. Bunnell, G. Promoff, and T. A. McAfee. 2016. Toking, vaping, and eating for health or fun: Marijuana use patterns. *American Journal of Preventive Medicine* 50(1):1–8.
- Sevigny, E. L., R. L. Pacula, and P. Heaton. 2014. The effects of medical marijuana laws on potency. *International Journal on Drug Policy* 25(2):308–319.
- Shafer Commission. 1972. *Marijuana: Signal of misunderstanding*. First Report of the National Commission on Marijuana and Drug Abuse. Washington, DC: U.S. Government Printing Office.
- UNODC (United Nations Office on Drugs and Crime). 2016. *World Drug Report 2016*. United Nations publication, Sales No. E.16.XI.7.

Part II

Therapeutic Effects

4

Therapeutic Effects of Cannabis and Cannabinoids

Chapter Highlights

- In adults with chemotherapy-induced nausea and vomiting, oral cannabinoids are effective antiemetics.
- In adults with chronic pain, patients who were treated with cannabis or cannabinoids are more likely to experience a clinically significant reduction in pain symptoms.
- In adults with multiple sclerosis (MS)-related spasticity, short-term use of oral cannabinoids improves patient-reported spasticity symptoms.
- For these conditions the effects of cannabinoids are modest; for all other conditions evaluated there is inadequate information to assess their effects.

Cannabis sativa has a long history as a medicinal plant, likely dating back more than two millennia (Russo et al., 2007). It was available as a licensed medicine in the United States for about a century before the American Medical Association removed it from the 12th edition of the *U.S. Pharmacopeia* (IOM, 1999). In 1985, pharmaceutical companies received approval to begin developing Δ^9 -tetrahydrocannabinol (THC) preparations—dronabinol and nabilone—for therapeutic use, and as a result, cannabinoids were reintroduced into the armamentarium of willing health care providers (Grotenhermen and Müller-Vahl, 2012). Efforts

are now being put into the trials of cannabidiol as a treatment for conditions such as epilepsy and schizophrenia,¹ although no such preparations have come to market at this time. Nabiximols, an oromucosal spray of a whole cannabis plant extract with a 1:1 ratio of THC to cannabidiol (CBD), was initially licensed and approved in Europe, the United Kingdom, and Canada for the treatment of pain and spasticity associated with multiple sclerosis (GW Pharmaceuticals, 2016; Pertwee, 2012), but it continues to undergo evaluation in Phase III clinical trials in the United States.² Efforts are under way to develop targeted pharmaceuticals that are agonists or antagonists of the cannabinoid receptors or that modulate the production and degradation of the endocannabinoids, although such interventions have not yet demonstrated safety or effectiveness. Nonetheless, therapeutic agents targeting cannabinoid receptors and endocannabinoids are expected to become available in the future.

The renewed interest in the therapeutic effects of cannabis emanates from the movement that began 20 years ago to make cannabis available as a medicine to patients with a variety of conditions. It was in 1996 that Arizona and California first passed medicinal cannabis legislation, although Arizona later rescinded the approval, so it would be California that paved the way. At the time that this report was written, in 2016, 28 states and the District of Columbia had legalized the medical use of cannabis; 8 states had legalized both medical and recreational use of cannabis; and another 16 states had allowed limited access to low-THC/high-CBD products (i.e., products with low levels of THC and high levels of CBD) (NCSL, 2016). A recent national survey showed that among current adult users, 10.5 percent reported using cannabis solely for medical purposes, and 46.6 percent reported a mixed medical/recreational use (Schauer et al., 2016). Of the states that allow for some access to cannabis compounds, cancer, HIV/AIDS, multiple sclerosis, glaucoma, seizures/epilepsy, and pain are among the most recognized qualifying ailments (Belendiuk et al., 2015; NCSL, 2016). There are certain states that provide more flexibility than others and that allow the use of medical cannabis for the treatment of any illness for which the drug provides relief for the individual. Given the steady liberalization of cannabis laws, the numbers of these states are likely to increase and therefore support the efforts to clarify the potential therapeutic benefits of medical cannabis on various health outcomes.

For example, the most common conditions for which medical cannabis is used in Colorado and Oregon are pain, spasticity associated with multiple sclerosis, nausea, posttraumatic stress disorder, cancer, epilepsy, cachexia, glaucoma, HIV/AIDS, and degenerative neurological

¹ ClinicalTrials.gov: NCT02447198, NCT02926859.

² ClinicalTrials.gov: NCT01361607.

conditions (CDPHE, 2016; OHA, 2016). We added to these conditions of interest by examining lists of qualifying ailments in states where such use is legal under state law. The resulting therapeutic uses covered by this chapter are chronic pain, cancer, chemotherapy-induced nausea and vomiting, anorexia and weight loss associated with HIV, irritable bowel syndrome, epilepsy, spasticity, Tourette syndrome, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, dystonia, dementia, glaucoma, traumatic brain injury, addiction, anxiety, depression, sleep disorders, posttraumatic stress disorder, and schizophrenia and other psychoses. The committee is aware that there may be other conditions for which there is evidence of efficacy for cannabis or cannabinoids. In this chapter, the committee will discuss the findings from 16 of the most recent, good- to fair-quality systematic reviews and 21 primary literature articles that best address the committee's research questions of interest.

As a reminder to the reader, several of the prioritized health endpoints discussed here in Part II are also reviewed in chapters of Part III; however, the research conclusions within these chapters may differ. This is, in part, due to differences in the study design of the evidence reviewed (e.g., randomized controlled trials [RCTs] versus epidemiological studies), differences in the characteristics of cannabis or cannabinoid exposure (e.g., form, dose, frequency of use), and the populations studied. As such, it is important that the reader is aware that this report was not designed to reconcile the proposed harms and benefits of cannabis or cannabinoid use across chapters.

CHRONIC PAIN

Relief from chronic pain is by far the most common condition cited by patients for the medical use of cannabis. For example, Light et al. (2014) reported that 94 percent of Colorado medical marijuana ID cardholders indicated "severe pain" as a medical condition. Likewise, Ilgen et al. (2013) reported that 87 percent of participants in their study were seeking medical marijuana for pain relief. In addition, there is evidence that some individuals are replacing the use of conventional pain medications (e.g., opiates) with cannabis. For example, one recent study reported survey data from patrons of a Michigan medical marijuana dispensary suggesting that medical cannabis use in pain patients was associated with a 64 percent reduction in opioid use (Boehnke et al., 2016). Similarly, recent analyses of prescription data from Medicare Part D enrollees in states with medical access to cannabis suggest a significant reduction in the prescription of conventional pain medications (Bradford and Bradford, 2016). Combined with the survey data suggesting that pain is one of the primary reasons for the use of medical cannabis, these recent reports sug-

gest that a number of pain patients are replacing the use of opioids with cannabis, despite the fact that cannabis has not been approved by the U.S. Food and Drug Administration (FDA) for chronic pain.

Are Cannabis or Cannabinoids an Effective Treatment for the Reduction of Chronic Pain?

Systematic Reviews

Five good- to fair-quality systematic reviews were identified. Of those five reviews, Whiting et al. (2015) was the most comprehensive, both in terms of the target medical conditions and in terms of the cannabinoids tested. Snedecor et al. (2013) was narrowly focused on pain related to spinal cord injury, did not include any studies that used cannabis, and only identified one study investigating cannabinoids (dronabinol). Two reviews on pain related to rheumatoid arthritis did not contribute unique studies or findings (Fitzcharles et al., 2016; Richards et al., 2012). Finally, one review (Andreae et al., 2015) conducted a Bayesian analysis of five primary studies of peripheral neuropathy that had tested the efficacy of cannabis in flower form administered via inhalation. Two of the primary studies in that review were also included in the Whiting review, while the other three were not. It is worth noting that the conclusions across all of the reviews were largely consistent in suggesting that cannabinoids demonstrate a modest effect on pain. For the purposes of this discussion, the primary source of information for the effect on cannabinoids on chronic pain was the review by Whiting et al. (2015). Whiting et al. (2015) included RCTs that compared cannabinoids to usual care, a placebo, or no treatment for 10 conditions. Where RCTs were unavailable for a condition or outcome, nonrandomized studies, including uncontrolled studies, were considered. This information was supplemented by a search of the primary literature from April 2015 to August 2016 as well as by additional context from Andreae et al. (2015) that was specific to the effects of inhaled cannabinoids.

The rigorous screening approach used by Whiting et al. (2015) led to the identification of 28 randomized trials in patients with chronic pain (2,454 participants). Twenty-two of these trials evaluated plant-derived cannabinoids (nabiximols, 13 trials; plant flower that was smoked or vaporized, 5 trials; THC oramucosal spray, 3 trials; and oral THC, 1 trial), while 5 trials evaluated synthetic THC (i.e., nabilone). All but 1 of the selected primary trials used a placebo control, while the remaining trial used an active comparator (amitriptyline). The medical condition underlying the chronic pain was most often related to a neuropathy (17 trials); other conditions included cancer pain, multiple sclerosis, rheuma-

toid arthritis, musculoskeletal issues, and chemotherapy-induced pain. Analyses across 7 trials that evaluated nabiximols and 1 that evaluated the effects of inhaled cannabis suggested that plant-derived cannabinoids increase the odds for improvement of pain by approximately 40 percent versus the control condition (odds ratio [OR], 1.41, 95% confidence interval [CI] = 0.99–2.00; 8 trials). The effects did not differ significantly across pain conditions, although it was not clear that there was adequate statistical power to test for such differences.

Only 1 trial ($n = 50$) that examined inhaled cannabis was included in the effect size estimates from Whiting et al. (2015). This study (Abrams et al., 2007) also indicated that cannabis reduced pain versus a placebo (OR, 3.43, 95% CI = 1.03–11.48). It is worth noting that the effect size for inhaled cannabis is consistent with a separate recent review of 5 trials of the effect of inhaled cannabis on neuropathic pain (Andreae et al., 2015). The pooled ORs from these trials contributed to the Bayesian pooled effect estimate of 3.22 for pain relief versus placebo (95% CI = 1.59–7.24) tested across 9 THC concentrations. There was also some evidence of a dose-dependent effect in these studies.

Primary Literature

In the addition to the reviews by Whiting et al. (2015) and Andreae et al. (2015), the committee identified two additional studies on the effect of cannabis flower on acute pain (Wallace et al., 2015; Wilsey et al., 2016). One of those studies found a dose-dependent effect of vaporized cannabis flower on spontaneous pain, with the high dose (7 percent THC) showing the strongest effect size (Wallace et al., 2015). The other study found that vaporized cannabis flower reduced pain but did not find a significant dose-dependent effect (Wilsey et al., 2016). These two studies are consistent with the previous reviews by Whiting et al. (2015) and Andreae et al. (2015), suggesting a reduction in pain after cannabis administration.

Discussion of Findings

The majority of studies on pain cited in Whiting et al. (2015) evaluated nabiximols outside the United States. In their review, the committee found that only a handful of studies have evaluated the use of cannabis in the United States, and all of them evaluated cannabis in flower form provided by the National Institute on Drug Abuse that was either vaporized or smoked. In contrast, many of the cannabis products that are sold in state-regulated markets bear little resemblance to the products that are available for research at the federal level in the United States. For exam-

ple, in 2015 between 498,170 and 721,599 units of medical and recreational cannabis edibles were sold per month in Colorado (Colorado DOR, 2016, p. 12). Pain patients also use topical forms (e.g., transdermal patches and creams). Thus, while the use of cannabis for the treatment of pain is supported by well-controlled clinical trials as reviewed above, very little is known about the efficacy, dose, routes of administration, or side effects of commonly used and commercially available cannabis products in the United States. Given the ubiquitous availability of cannabis products in much of the nation, more research is needed on the various forms, routes of administration, and combination of cannabinoids.

CONCLUSION 4-1 There is substantial evidence that cannabis is an effective treatment for chronic pain in adults.

CANCER

Cancer is a broad term used to describe a wide range of related diseases that are characterized by an abnormal, unregulated division of cells; it is a biological disorder that often results in tumor growth (NCI, 2015). Cancer is among the leading causes of mortality in the United States, and by the close of 2016 there will be an estimated 1.7 million new cancer diagnoses (NCI, 2016). Relevant to the committee's interest, there is evidence to suggest that cannabinoids (and the endocannabinoid system more generally) may play a role in the cancer regulation processes (Rocha et al., 2014). Therefore, there is interest in determining the efficacy of cannabis or cannabinoids for the treatment of cancer.

Are Cannabis or Cannabinoids an Effective Treatment for Cancer?

Systematic Reviews

Using the committee's search strategy only one recent review was found to be of good to fair quality (Rocha et al., 2014).³ The review focused exclusively on the anti-tumor effects of cannabinoids on gliomas.⁴ Of the 2,260 studies identified through December 2012, 35 studies met the inclusion criteria. With the exception of a small clinical trial, these studies

³ Due to the lack of recent, high-quality reviews, the committee has identified that a research gap exists concerning the effectiveness of cannabis or cannabinoids in treating cancer in general.

⁴ Glioma is a type of tumor that originates in the central nervous system (i.e., the brain or spine) and arises from glial cells.

were all preclinical studies. All 16 of the in vivo studies found an anti-tumor effect of cannabinoids.

Primary Literature

The committee did not identify any good-quality primary literature that reported on cannabis or cannabinoids for the treatment of cancer that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

Clearly, there is insufficient evidence to make any statement about the efficacy of cannabinoids as a treatment for glioma. However, the signal from the preclinical literature suggests that clinical research with cannabinoids needs to be conducted.

CONCLUSION 4-2 There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancers, including glioma.

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Nausea and vomiting are common side effects of many cytotoxic chemotherapy agents. A number of pharmaceutical interventions in various drug classes have been approved for the treatment of chemotherapy-induced nausea and vomiting. Among the cannabinoid medications, nabilone and dronabinol were initially approved in 1985 for nausea and vomiting associated with cancer chemotherapy in patients who failed to respond adequately to conventional antiemetic treatments (Todaro, 2012, pp. 488, 490).

Are Cannabis or Cannabinoids an Effective Treatment for the Reduction of Chemotherapy-Induced Nausea and Vomiting?

Systematic Reviews

Whiting et al. (2015) summarized 28 trials reporting on nausea and vomiting due to chemotherapy, most published before 1984, involving 1,772 participants. The cannabinoid therapies investigated in these trials included nabilone (14), tetrahydrocannabinol (6), levonantradol (4), dronabinol (3), and nabiximols (1). Eight studies were placebo controlled,

and 20 included active comparators (prochlorperazine 15; chlorpromazine 2; domperidone 2; and alizapride, hydroxyzine, metoclopramide, and ondansetron 1 each). Two studies evaluated combinations of dronabinol with prochlorperazine or ondansetron. The average number of patients showing a complete nausea and vomiting response was greater with cannabinoids than the placebo (OR, 3.82, 95% CI = 1.55–9.42) in 3 trials of dronabinol and nabilone that were considered low-quality evidence. Whiting et al. (2015) concluded that all trials suggested a greater benefit for cannabinoids than for both active agents and for the placebo, although these did not reach statistical significance in all trials.

Of the 23 trials summarized in a Cochrane review (Smith et al., 2015), 19 were crossover design and 4 were parallel-group design. The cannabinoids investigated were nabilone (12) or dronabinol (11), with 9 placebo-controlled trials (819 participants) and 15 with active comparators (prochlorperazine, 11; metoclopramide, 2; chlorpromazine, 1; domperidone, 1). In 2 trials, a cannabinoid added to a standard antiemetic was compared to the standard alone. While 2 of the placebo-controlled trials showed no significant difference in those reporting absence of nausea with cannabinoids (relative risk [RR], 2.0, 95% CI = 0.19–21), 3 showed a greater chance of having complete absence of vomiting with cannabinoids (RR, 5.7, 95% CI = 2.16–13) and 3 showed a numerically higher chance of complete absence of both nausea and vomiting (RR, 2.9, 95% CI = 1.8–4.7). There was no difference in outcome between patients who were cannabis-naïve and those who were not (P value = 0.4). Two trials found a patient preference for cannabinoids over the comparator. When compared to prochlorperazine, there was no significant difference in the control of nausea, vomiting, or both, although in 7 of the trials there was a higher chance of patients reporting a preference for the cannabinoid therapy (RR, 3.2, 95% CI = 2.2–4.7). In their review the investigators state that cannabinoids were highly effective, being more efficacious than the placebo and similar to conventional antiemetics in treating chemotherapy-induced nausea and vomiting. Despite causing more adverse events such as dizziness, dysphoria, euphoria, “feeling high,” and sedation, there was weak evidence for a preference for cannabinoids over the placebo and stronger evidence for a preference over other antiemetics. Despite these findings, however, the authors concluded that there was no evidence to support the use of cannabinoids over current first-line antiemetic therapies and that cannabinoids should be considered as useful adjunctive treatment “for people on moderately or highly emetogenic chemotherapy that are refractory to other antiemetic treatments, when all other options have been tried” (Smith et al., 2015, p. 23).

Only 3 of the 28 trials in a systematic review of antiemetic therapies in children receiving chemotherapy involved cannabinoid therapies

(nabilone 2; THC 1) (Phillips et al., 2016). The comparators were prochlorperazine in the first nabilone trial, domperidone in the second, and prochlorperazine and metoclopramide in two separate randomizations in the THC trial. In 1 trial with unclear risk of bias, THC dosed at 10 mg/m² five times on the day of chemotherapy was superior to prochlorperazine in the complete control of acute nausea (RR, 20.7, 95% CI = 17.2–36.2) and vomiting (RR, 19.0, 95% CI = 13.7–26.3). Another trial reported better nausea severity scores for nabilone compared to domperidone (1.5 versus 2.5 on a 0 to 3 [none to worst] scale) ($p = 0.01$). The largest and most recent trial in this review compared THC to prochlorperazine and found no benefit over the control on emesis (RR, 1.0, 95% CI = 0.85–1.17).

Primary Literature

An additional search of the primary literature since the review by Whiting et al. (2015) did not identify any additional studies. The primary literature was then searched in an effort to find studies of cannabinoids compared to the more widely used antiemetics. One trial conducted in 2007 investigated a cannabinoid therapy compared to the current generation of serotonin antagonist antiemetics, as opposed to the dopamine D2 receptor antagonists used in the earlier trials. This 64-patient study evaluated the frequently used antiemetic ondansetron versus dronabinol versus the combination of the two in delayed chemotherapy-induced nausea and vomiting (Meiri et al., 2007). The two agents appeared similar in their effectiveness, with no added benefit from the combination. Hence, the cannabinoid again fared as well as the current standard antiemetic in this more recent investigation.

Discussion of Findings

The oral THC preparations nabilone and dronabinol have been available for the treatment of chemotherapy-induced nausea and vomiting for more than 30 years (Grotenhermen and Müller-Vahl, 2012). They were both found to be superior to the placebo and equivalent to the available antiemetics at the time that the original trials were conducted. A more recent investigation suggests that dronabinol is equivalent to ondansetron for delayed nausea and vomiting, although no comparison to the currently more widely used neurokinin-1 inhibitors has been conducted. In the earlier trials, patients reported a preference for the cannabinoids over available agents. Despite an abundance of anecdotal reports of the benefits of plant cannabis, either inhaled or ingested orally, as an effective treatment for chemotherapy-induced nausea and vomiting, there are no good-quality randomized trials investigating this option. This is,

in part, due to the existing obstacles to investigating the potential therapeutic benefit of the cannabis plant. Nor have any of the reviewed trials investigated the effectiveness of cannabidiol or cannabidiol-enriched cannabis in chemotherapy-induced nausea and vomiting. Such information is frequently requested by patients seeking to control chemotherapy-induced nausea and vomiting without the psychoactive effects of the THC-based preparations. Resolving this identified research gap may be a future research priority.

CONCLUSION 4-3 There is conclusive evidence that oral cannabinoids are effective antiemetics in the treatment of chemotherapy-induced nausea and vomiting.

ANOREXIA AND WEIGHT LOSS

Anorexia and weight loss are common side effects of many diseases, especially cancer. And prior to the availability of highly active antiretroviral therapy, a wasting syndrome was a frequent clinical manifestation in patients with human immunodeficiency virus (HIV) infection and advanced acquired immune deficiency syndrome (AIDS). The labeled indications for dronabinol were expanded in 1992 to include treatment of anorexia associated with weight loss in patients with AIDS (IOM, 1999, p. 156).

Are Cannabis or Cannabinoids an Effective Treatment for Anorexia and Weight Loss Associated with HIV/AIDS, Cancer-Associated Anorexia-Cachexia Syndrome, and Anorexia Nervosa?

AIDS Wasting Syndrome

Systematic Reviews Two good-quality systematic reviews included trials investigating cannabinoid therapies in patients with HIV/AIDS. Four randomized controlled trials involving 255 patients were assessed by Whiting et al. (2015), who described all of the trials to be at high risk of bias (ROB) for reasons not elaborated.⁵ All four studies included dronabinol, with one investigating inhaled cannabis as well. Three trials were placebo-controlled, and one used the progestational agent megestrol acetate as the comparator. The review authors concluded that there was some evidence suggesting that cannabinoids were effective in weight gain

⁵ Key issues that led to high ROB ratings were: high (n = 1) or unclear (n = 3) ROB for allocation concealment; unclear ROB (n = 3) for blinded outcome assessments; high (n = 1) or unclear (n = 1) ROB for randomization.

in HIV. A second systematic review focused on morbidity and mortality in HIV/AIDS as the primary outcomes, with changes in appetite and weight as secondary endpoints (Lutge et al., 2013). Seven RCTs conducted between 1993 and 2009 were included in the qualitative analysis. The trials compared dronabinol or inhaled cannabis with a placebo or with each other. In one study the individuals' weights increased significantly more ($p < 0.01$) on higher doses of cannabis (3.9 percent THC) and dronabinol (10 mg) than on lower doses. In a second trial, median weight was increased with inhaled cannabis (3.5 percent) by 3.0 kg ($p = 0.021$) and dronabinol (2.5 mg) by 3.2 kg ($p = 0.004$) when compared with a placebo (a 1.1-kg increase over a 21-day exposure). In a study with 88 evaluable patients, the dronabinol group gained an average of 0.1 kg, while the placebo recipients lost a mean of 0.4 kg ($p = 0.14$). The proportion of patients gaining at least 2 kg was the same in both groups. Most of the weight gain was in the body fat compartment when this was investigated. Changes in appetite, food, and caloric intake were not deemed to be evaluable in any of the studies. These investigators concluded that the evidence for the efficacy and safety of cannabis and cannabinoids is lacking to support utility in treating AIDS-associated anorexia.

Primary Literature The committee did not identify any good-quality primary literature that reported on cannabis or cannabinoids as effective treatments for AIDS wasting syndrome that were published subsequently to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question. This is largely due to the virtual disappearance of the syndrome since effective antiretroviral therapies became available in the mid-1990s.

Cancer-Associated Anorexia-Cachexia Syndrome

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on cannabis or cannabinoids as effective treatments for cancer-associated anorexia-cachexia syndrome.

Primary Literature A Phase III multicenter, randomized, double-blind placebo-controlled trial was conducted by the Cannabis-In-Cachexia-Study-Group in patients with cancer-related anorexia-cachexia syndrome (Strasser et al., 2006). Patients with advanced cancer and weight loss of greater than 5 percent over 6 months were randomized 2:2:1 to receive treatment with a cannabis extract (standardized to THC 2.5 mg and cannabidiol 1.0 mg), THC 2.5 mg, or a placebo twice daily for 6 weeks. Appetite, mood, and nausea were monitored daily. Cancer-related quality of life and cannabinoid-related toxicity were also monitored. Only 164 of

the 243 patients who were randomized completed the trial. An intent-to-treat analysis yielded no difference between the groups in appetite, quality of life, or toxicity. Increased appetite was reported by 73 percent of the cannabis-extract, 58 percent of the THC group, and 69 percent of the placebo recipients. Recruitment was terminated early by the data review board because it was believed to be unlikely that differences would emerge between the treatment arms. The findings in this study reinforce the results from an earlier trial investigating dronabinol, megestrol acetate, or the combination in 469 advanced cancer patients with a loss of appetite and greater than 5 pounds weight loss over the prior 2 months (Jatoi et al., 2002). Megestrol acetate was superior to dronabinol for the improvement of both appetite and weight, with the combination therapy conferring no additional benefit. Seventy-five percent of the megestrol recipients reported an improvement in appetite compared to 49 percent of those receiving dronabinol ($p = 0.0001$). Of those in the combination arm, 66 percent reported improvement. A weight gain greater than or equal to 10 percent over their baseline at some point during the course of the trial was reported by 11 percent of those in the megestrol arm, compared with 3 percent of the dronabinol recipients ($p = 0.02$). The combination arm reported a weight gain in 8 percent. These findings confirm a similarly designed trial that was conducted in patients with AIDS wasting syndrome (Timpone et al., 1997).

Anorexia Nervosa

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on medical cannabis as an effective treatment for anorexia nervosa.

Primary Literature Pharmacological interventions in the treatment of anorexia nervosa have not been promising to date. Andries et al. (2014) conducted a prospective, randomized, double-blind, controlled crossover trial in 24 women with anorexia nervosa of at least 5 years' duration attending both psychiatric and somatic therapy as inpatients or outpatients. In addition to their standard psychotherapy and nutritional interventions, the participants received dronabinol 2.5 mg twice daily for 4 weeks and a matching placebo for 4 weeks, randomly assigned to two treatment sequences (dronabinol/placebo or placebo/dronabinol). The primary outcome was weight change assessed weekly. The secondary outcome was change in Eating Disorder Inventory-2 (EDI-2) scores. The participants had a significant weight gain of 1.00 kg (95% CI = 0.40–1.62) during dronabinol therapy and 0.34 kg (95% CI = –0.14–0.82) during the placebo ($p = 0.03$). No statistically different differences in EDI-2 score

changes were seen during treatment with dronabinol or the placebo, suggesting that there was no real effect on the participants' attitudinal and behavioral traits related to eating disorders. The authors acknowledged the small sample size and the short duration of exposure, as well as the potential psychogenic effects, but they concluded that low-dose dronabinol is a safe adjuvant palliative therapy in a highly selected subgroup of chronically undernourished women with anorexia nervosa.

Discussion of Findings

There is some evidence for oral cannabinoids being able to increase weight in patients with the HIV-associated wasting syndrome and anorexia nervosa. No benefit has been demonstrated in cancer-associated anorexia-cachexia syndrome. The studies have generally been small and of short duration and may not have investigated the optimal dose of the cannabinoid. In one study in HIV patients, both dronabinol and inhaled cannabis increased weight significantly compared to the placebo dronabinol. Cannabis has long been felt to have an orexigenic effect, increasing food intake (Abel, 1975). Small residential studies conducted in the 1980s found that inhaled cannabis increased caloric intake by 40 percent, with most of the increase occurring as snacks and not during meals (Foltin et al., 1988). Hence, the results of the clinical trials in AIDS wasting and cancer-associated anorexia-cachexia syndrome demonstrating little to no impact on appetite and weight were somewhat unexpected. One could postulate that perhaps other components of the plant in addition to THC may contribute to the effect of cannabis on appetite and food intake. There have not been any randomized controlled trials conducted studying the effect of plant-derived cannabis on appetite and weight with weight as the primary endpoint. This is, in part, due to existing obstacles to investigating the potential therapeutic benefit of the cannabis plant.

CONCLUSION 4-4

- 4-4(a) There is limited evidence that cannabis and oral cannabinoids are effective in increasing appetite and decreasing weight loss associated with HIV/AIDS.**
- 4-4(b) There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancer-associated anorexia-cachexia syndrome and anorexia nervosa.**

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder commonly associated with symptoms of abdominal cramping and changes in bowel movement patterns. Irritable bowel syndrome is classified into four types based on the types of bowel movements: IBS with diarrhea, IBS with constipation, IBS mixed, and IBS unclassified (NIDDK, 2015). Approximately 11 percent of the world's population suffers from at least one type of this disorder (Canavan et al., 2014).

Type 1 cannabinoid (CB₁) receptors are present in the mucosa and neuromuscular layers of the colon; they are also expressed in plasma cells and influence mucosal inflammation (Wright et al., 2005). In animal models, endocannabinoids acting on CB₁ receptors inhibit gastric and small intestinal transit and colonic propulsion (Pinto et al., 2002). Studies in healthy volunteers have shown effects on gastric motility and colonic motility (Esfandyari et al., 2006). Thus, cannabinoids have the potential for therapeutic effect in patients with IBS (Wong et al., 2012).

Are Cannabis or Cannabinoids an Effective Treatment for the Symptoms of Irritable Bowel Syndrome?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on medical cannabis as an effective treatment for symptoms of irritable bowel syndrome.

Primary Literature

We identified a single relevant trial (Wong et al., 2012) evaluating dronabinol in patients with irritable bowel syndrome with diarrhea (IBS-D). This low-risk-of-bias trial enrolled 36 patients between the ages of 18 and 69 with IBS-D. Patients were randomized to dronabinol 2.5 mg BID⁶ (n = 10), dronabinol 5 mg BID (n = 13), or a placebo (n = 13) for 2 days. No overall treatment effects of dronabinol on gastric, small bowel, or colonic transit, as measured by radioscintigraphy, were detected.

Discussion of Findings

A single, small trial found no effect of two doses of dronabinol on gastrointestinal transit. The quality of evidence for the finding of no effect

⁶ BID is an abbreviation for the Latin phrase *bis in die*, which means twice per day.

for irritable bowel syndrome is insufficient based on the short treatment duration, small sample size, short-term follow-up, and lack of patient-reported outcomes. Trials that evaluate the effects of cannabinoids on patient-reported outcomes are needed to further understand the clinical effects in patients with IBS.

CONCLUSION 4-5 There is insufficient evidence to support or refute the conclusion that dronabinol is an effective treatment for the symptoms of irritable bowel syndrome.

EPILEPSY

Epilepsy refers to a spectrum of chronic neurological disorders in which clusters of neurons in the brain sometimes signal abnormally and cause seizures (NINDS, 2016a). Epilepsy disorder affects an estimated 2.75 million Americans, across all age ranges and ethnicities (NINDS, 2016a). Although there are many antiepileptic medications currently on the market, about one-third of persons with epilepsy will continue to have seizures even when treated (Mohanraj and Brodie, 2006). Both THC and CBD can prevent seizures in animal models (Devinsky et al., 2014).

Are Cannabis or Cannabinoids an Effective Treatment for the Symptoms of Epilepsy?

Systematic Reviews

We identified two systematic reviews of randomized trials assessing the efficacy of cannabis or cannabinoids, used either as monotherapy or in addition to other therapies, in reducing seizure frequency in persons with epilepsy. Gloss and Vickrey (2014) published a systematic review of randomized controlled trials. They identified four reports (including one conference abstract and one letter to the editor) of cannabinoid trials, all of which they considered to be of low quality. Combined, the trials included a total of 48 patients. The systematic review's primary prespecified outcome was freedom from seizures for either 12 months or three times the longest previous seizure-free interval. None of the four trials assessed this endpoint. Accordingly, Gloss and Vickrey asserted that no reliable conclusions could be drawn regarding the efficacy of cannabinoids for epilepsy.

Koppel et al. (2014) published a fair-quality systematic review. They identified no high-quality randomized trials and concluded that the existing data were insufficient to support or refute the efficacy of cannabinoids for reducing seizure frequency.

Primary Literature

We identified two case series that reported on the experience of patients treated with cannabidiol for epilepsy that were published subsequent to the systematic reviews described above. The first of these was an open-label, expanded-access program of oral cannabidiol with no concurrent control group in patients with severe, intractable childhood-onset epilepsy that was conducted at 11 U.S. epilepsy centers and reported by Devinsky et al. (2016) and by Rosenberg et al. (2015). Devinsky et al. (2016) reported on 162 patients ages 1 to 30 years; Rosenberg et al. (2015) reported on 137 of these patients. The median monthly frequency of motor seizures was 30.0 (interquartile range [IQR] 11.0–96.0) at baseline and 15.8 (IQR 5.6–57.6) over the 12-week treatment period. The median reduction in motor seizures while receiving cannabidiol in this uncontrolled case series was 36.5 percent (IQR 0–64.7).

Tzadok et al. (2016) reported on the unblinded experience of Israeli pediatric epilepsy clinics treating 74 children and adolescents with intractable epilepsy with an oral formulation of cannabidiol and tetrahydrocannabinol at a 20:1 ratio for an average of 6 months. There was no concurrent control group. Compared with baseline, 18 percent of children experienced a 75–100 percent reduction in seizure frequency, 34 percent experienced a 50–75 percent reduction, 12 percent reported a 25–50 percent reduction, 26 percent reported a reduction of less than 25 percent, and 7 percent reported aggravation of seizures that led to a discontinuation of the cannabinoid treatment.

The lack of a concurrent placebo control group and the resulting potential for regression to the mean and other sources of bias greatly reduce the strength of conclusions that can be drawn from the experiences reported by Devinsky et al. (2016), Rosenberg et al. (2015), and Tzadok et al. (2016) about the efficacy of cannabinoids for epilepsy. Randomized trials of the efficacy of cannabidiol for different forms of epilepsy have been completed,⁷ but their results have not been published at the time of this report.

Discussion of Findings

Recent systematic reviews were unable to identify any randomized controlled trials evaluating the efficacy of cannabinoids for the treatment of epilepsy. Currently available clinical data therefore consist solely of uncontrolled case series, which do not provide high-quality evidence

⁷ ClinicalTrials.gov: NCT02224560, NCT02224690, NCT02091375, NCT02324673.

of efficacy. Randomized trials of the efficacy of cannabidiol for different forms of epilepsy have been completed and await publication.

CONCLUSION 4-6 There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for epilepsy.

SPASTICITY ASSOCIATED WITH MULTIPLE SCLEROSIS OR SPINAL CORD INJURY

Spasticity is defined as disordered sensorimotor control resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles (Pandyan et al., 2005). It occurs in some patients with chronic neurological conditions such as multiple sclerosis (MS) and paraplegia due to spinal cord injury. Recent studies have shown that some individuals with MS are seeking alternative therapies, including cannabis, to treat symptoms associated with MS (Zajicek et al., 2012).

Are Cannabis or Cannabinoids an Effective Treatment for Spasticity Associated with Multiple Sclerosis or Spinal Cord Injury?

Systematic Reviews

We identified two recent systematic reviews that assessed the efficacy of cannabis or cannabinoids in treating muscle spasticity in patients with MS or paraplegia due to spinal cord injury—the systematic review by Whiting et al. (2015) that examined evidence for a broad range of medical uses of cannabis or cannabinoids and the systematic review by Koppel et al. (2014) that focused more narrowly on neurologic conditions. Both systematic reviews examined only randomized, placebo-controlled trials. Whiting et al. (2015) excluded from their primary analysis trials that did not use a parallel group design (i.e., they excluded crossover trials) and performed a quantitative pooling of results. In contrast, Koppel et al. (2014) included crossover trials but did not perform a quantitative pooling of results.

Whiting et al. (2015) searched for studies examining the efficacy of cannabinoids for spasticity due to MS or paraplegia. They identified 11 studies that included patients with MS and 3 that included patients with paraplegia caused by spinal cord injury. None of the studies in patients with paraplegia caused by spinal cord injury were reported as full papers or included sufficient data to allow them to be included in pooled estimates. Whiting et al. (2015) reported that in their pooled analysis of three

trials in patients with MS, nabiximols and nabilone were associated with an average change (i.e., improvement) in spasticity rating assessed by a patient-reported numeric rating scale of -0.76 (95% CI = -1.38 to -0.14) on a 0 to 10 scale that was statistically greater than for the placebo. They further reported finding no evidence for a difference according to type of cannabinoid (i.e., nabiximols versus nabilone). Whiting et al. (2015) also reported that the pooled odds of patient-reported improvement on a global impression-of-change score was greater with nabiximols than with the placebo (OR, 1.44, 95% CI = 1.07–1.94).

The review by Koppel et al. (2014) restricted its focus on spasticity to that due to MS. Their conclusions were broadly in agreement with corresponding conclusions from the review by Whiting et al. (2015). In particular, Koppel et al. (2014) concluded that in patients with MS, nabiximols and orally administered THC are “probably effective” for reducing patient-reported spasticity scores and that oral cannabis extract is “established as effective for reducing patient-reported scores” for spasticity (Koppel et al., 2014, p. 1558).

A commonly used scale for rating spasticity is the Ashworth scale (Ashworth, 1964). However, this scale has been criticized as unreliable, insensitive to therapeutic benefit, and reflective only of passive resistance to movement and not of other features of spasticity (Pandyan et al., 1999; Wade et al., 2010). Furthermore, no minimally important difference in the Ashworth scale has been established. Whiting et al. (2015) calculated a pooled measure of improvement on the Ashworth scale versus placebo based on five parallel-group-design trials. They reported that nabiximols, dronabinol, and oral THC/CBD were associated with a numerically greater average improvement on the Ashworth scale than with a placebo but that this difference was not statistically significant. This conclusion is in broad agreement with corresponding conclusions reached by Koppel et al. (2014), who concluded in particular that nabiximols, oral cannabis extract and orally administered THC are “probably ineffective” for reducing objective measures of spasticity in the short term (6–15 weeks), although oral cannabis extract and orally administered THC are “possibly effective” for objective measures at 1 year.

Primary Literature

An additional placebo-controlled crossover trial of nabiximols for the treatment of spasticity in patients with MS was published after the period covered by the Whiting and Koppel systematic reviews (Leocani et al., 2015). This study randomized 44 patients but analyzed only 34 because of post-randomization exclusions and dropouts. Such post-randomization exclusions and dropouts reduce the strength of the evidence that is pro-

vided by this study. Patient-reported measures of spasticity were not assessed. After 4 weeks of treatment, response on the modified Ashworth scale (defined as improvement of at least 20 percent) was more common in the THC/CBD group (50 percent) than in the placebo group (23.5 percent), $p = 0.041$.

Discussion of Findings

Based on evidence from randomized controlled trials included in systematic reviews, an oral cannabis extract, nabiximols, and orally administered THC are probably effective for reducing patient-reported spasticity scores in patients with MS. The effect appears to be modest, as reflected by an average reduction of 0.76 units on a 0 to 10 scale. These agents have not consistently demonstrated a benefit on clinician-measured spasticity indices such as the modified Ashworth scale in patients with MS. Given the lack of published papers reporting the results of trials conducted in patients with spasticity due to spinal cord injury, there is insufficient evidence to conclude that cannabinoids are effective for treating spasticity in this population.

CONCLUSION 4-7

4-7(a) There is substantial evidence that oral cannabinoids are an effective treatment for improving patient-reported multiple sclerosis spasticity symptoms, but limited evidence for an effect on clinician-measured spasticity.

4-7(b) There is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for spasticity in patients with paralysis due to spinal cord injury.

TOURETTE SYNDROME

Tourette syndrome is a neurological disorder characterized by sporadic movements or vocalizations commonly called “tics” (NINDS, 2014). While there is currently no cure for Tourette syndrome, recent efforts have explored whether cannabis may be effective in reducing symptoms commonly associated with the disorder (Koppel et al., 2014).

Are Cannabis or Cannabinoids an Effective Treatment for the Symptoms Associated with Tourette Syndrome?

Systematic Reviews

We identified two good-quality systematic reviews (Koppel et al., 2014; Whiting et al., 2015) that evaluated medical cannabis for Tourette syndrome. Both good-quality reviews identified the same trials, and we focus on the more recent review by Whiting et al. (2015). The two RCTs (four reports), conducted by the same research group (Müller-Vahl et al., 2001, 2002, 2003a,b), compared THC capsules (maximum dose 10 mg daily) to a placebo in 36 patients with Tourette syndrome. Tic severity, assessed by multiple measures, and global clinical outcomes were improved with THC capsules. On a 0 to 6 severity scale, symptoms were improved by less than 1 point. These outcomes were assessed at 2 days (unclear-risk-of-bias trial) and 6 weeks (high-risk-of-bias trial). Neither trial described randomization or allocation concealment adequately, and the 6-week trial was rated high risk of bias for incomplete outcome data.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for Tourette syndrome, and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

No clear link has been established between symptoms of Tourette syndrome and cannabinoid sites or mechanism of action. However, case reports have suggested that cannabis can reduce tics and that the therapeutic effects of cannabis might be due to the anxiety-reducing properties of marijuana rather than to a specific anti-tic effect (Hemming and Yellowlees, 1993; Sandyk and Awerbuch, 1988). Two small trials (assessed as being of fair to poor quality) provide limited evidence for the therapeutic effects of THC capsules on tic severity and global clinical outcomes.

CONCLUSION 4-8 There is limited evidence that THC capsules are an effective treatment for improving symptoms of Tourette syndrome.

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting the motor neurons in the spinal cord, brain stem, and motor cortex, ultimately leading to complete paralysis (Rossi et al., 2010). The pathogenesis of ALS remains unclear, but the disease is thought to result from the interplay of a number of mechanisms, including neurofilament accumulation, excitotoxicity, oxidative stress, and neuroinflammation (Redler and Dokholyan, 2012), all of which may be amenable to manipulation of the endocannabinoid system and cannabinoid receptors.

Are Cannabis or Cannabinoids an Effective Treatment for the Symptoms Associated with Amyotrophic Lateral Sclerosis?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on medical cannabis as an effective treatment for symptoms associated with amyotrophic lateral sclerosis.

Primary Literature

On the basis of proposed pathogenesis and anecdotal reports of symptomatic benefit from the use of cannabis in patients with ALS, two small trials of dronabinol have been conducted. In a randomized, double-blind crossover study, 19 patients with ALS were treated with dronabinol doses of 2.5 to 10 mg daily for 4 weeks (Gelinas et al., 2002). Participants noted improvement in appetite and sleep but not in cramps or fasciculations (involuntary muscle twitches). The second study enrolled 27 patients with ALS who had moderate to severe cramps (greater than 4 on a 0–10 visual analogue scale) in a randomized, double-blind trial of dronabinol 5 mg twice daily or a placebo, each given for 2 weeks with an intervening 2-week washout period (Weber et al., 2010). The primary endpoint was a change in cramp intensity with secondary endpoints of change in cramp number, intensity of fasciculations, quality of life, sleep, appetite, and depression. There was no difference between dronabinol and the placebo seen in any of the endpoints. The investigators reported that the dronabinol was very well tolerated and postulated that the dronabinol dose may have been too low as well as suggesting that a carryover effect in the crossover design may have obfuscated any differences in the treatment arms. The sample size was too small to discern anything but a large effect.

Discussion of Findings

Two small studies investigated the effect of dronabinol on symptoms associated with ALS. Although there were no differences from placebo in either trial, the sample sizes were small, the duration of the studies was short, and the dose of dronabinol may have been too small to ascertain any activity. The effect of cannabis was not investigated.

CONCLUSION 4-9 There is insufficient evidence that cannabinoids are an effective treatment for symptoms associated with amyotrophic lateral sclerosis.

HUNTINGTON'S DISEASE

Huntington's disease is characterized by chorea (abnormal, involuntary movement) along with cognitive decline and psychiatric impairment (Armstrong and Miyasaki, 2012). Worsening chorea significantly impacts patient quality of life. The pathophysiology and neurochemical basis of Huntington's disease are incompletely understood. Neuroprotective trials often investigate agents that may decrease oxidative stress or glutamatergic changes related to excitotoxic stress. There is some preclinical evidence and limited clinical evidence that suggest that changes in the endocannabinoid system may be linked to the pathophysiology of Huntington's disease (Pazos et al., 2008; van Laere et al., 2010).

**Are Cannabis or Cannabinoids an Effective Treatment
for the Motor Function and Cognitive Performance
Associated with Huntington's Disease?**

Systematic Reviews

The systematic review from the American Academy of Neurology includes two studies on Huntington's disease (Koppel et al., 2014). A randomized, double-blind, placebo-controlled crossover pilot trial investigated nabilone 1 or 2 mg daily for 5 weeks followed by a placebo in 22 patients with symptomatic Huntington's disease (Curtis et al., 2009). An additional 22 patients were randomized to the placebo followed by nabilone. The primary endpoint was the total motor score of the Unified Huntington's Disease Rating Scale (UHDRS). Secondary endpoints included the chorea, cognitive performance, and psychiatric changes measured with the same instrument. No significant difference in the total motor score was seen in the 37 evaluable patients (treatment difference, 0.86, 95% CI = -1.8-3.52), with a 1-point change considered clinically significant. There was evidence of an improvement in the chorea subscore

with nabilone (treatment difference, 1.68, 95% CI = 0.44–2.92). There was no difference between treatments for cognition, but there was evidence of an improvement in the two neuropsychiatric outcome measures in the nabilone arm—UHDRS behavioral assessment (4.01, 95% CI = –0.11–8.13) and neuropsychiatric inventory (6.43, 95% CI = 0.2–12.66). The small estimated treatment effect with wide confidence intervals reduces the level of evidence for nabilone’s effectiveness from this pilot study. However, based on this trial, the American Academy of Neurology guideline concluded that “nabilone possibly modestly improves Huntington’s disease chorea” (Armstrong and Miyasaki, 2012, p. 601). The second study included in the systematic review was a lower-quality, 15-patient randomized, double-blind, placebo-controlled trial investigating the effect of cannabidiol capsules at a dose of 10 mg/kg/day in two divided doses (Consroe et al., 1991). The endpoints in this study involving patients with Huntington’s disease who were not on neuroleptics were chorea severity, functional limitations, and side effects. There were no statistically significant differences between cannabidiol and placebo in any outcomes, although the American Academy of Neurology considered the study to be underpowered.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for the declines in motor function and cognitive performance associated with Huntington’s disease that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

Two small studies have investigated the potential benefit of cannabinoids in patients with Huntington’s disease. Although nabilone appeared to have some potential benefit on chorea, cannabidiol appeared to be equal to placebo in ameliorating symptoms. Both studies were of short duration and likely underpowered because of their small sample sizes. Cannabis has not been investigated in Huntington’s disease.

CONCLUSION 4-10 There is insufficient evidence to support or refute the conclusion that oral cannabinoids are an effective treatment for chorea and certain neuropsychiatric symptoms associated with Huntington’s disease.

PARKINSON'S DISEASE

Parkinson's disease is a motor system disorder attributed to the loss of dopamine-producing brain cells. It is characterized clinically by tremor, rigidity, bradykinesia (slowness of movement), and impaired balance and coordination (PDF, 2016a). An estimated 60,000 Americans are diagnosed with this disorder each year (PDF, 2016b).

Although the disease is progressive and without cure, there are medications that can ameliorate some of the associated symptoms. Although levodopa has demonstrated efficacy for treating symptoms of Parkinson's disease, long-term use of levodopa is associated with the development of side effects, especially dyskinesias (involuntary movements) (NINDS, 2015). Evidence suggests that the endocannabinoid system plays a meaningful role in certain neurodegenerative processes (Krishnan et al., 2009); thus, it may be useful to determine the efficacy of cannabinoids in treating the symptoms of neurodegenerative diseases.

Are Cannabis or Cannabinoids an Effective Treatment for the Motor System Symptoms Associated with Parkinson's Disease or the Levodopa-Induced Dyskinesia?

Systematic Reviews

The systematic review of cannabis in selected neurologic disorders (Koppel et al., 2014) identified two trials of cannabinoid therapies in patients with levodopa-induced dyskinesias. Nineteen patients with levodopa-induced dyskinesia greater than or equal to 2 as determined by questions 32–34 of the Unified Parkinson's Disease Rating Scale (UPDRS) were randomized in a double-blind, placebo-controlled crossover trial to receive Cannador capsules (containing THC 2.5 mg and CBD 1.25 mg) to a maximum dose of 0.25 mg/kg of THC daily or placebo (Carroll et al., 2004). The primary endpoint was the effect of treatment on the dyskinesia score of the UPDRS. Secondary endpoints included the impact of dyskinesia on function, pathophysiologic indicators of dyskinesia, duration of dyskinesia, quality of life, sleep, pain, and overall severity of Parkinson's disease. The overall treatment effect was +0.52, which indicated a worsening with Cannador, although this worsening was not statistically significant ($p = 0.09$). No effects were seen on the secondary outcomes. Although there were more adverse events on the drug than on the placebo, the investigators felt that the treatment was well tolerated. The study had limited statistical power to detect anything but a large treatment effect due to its small sample size. The second study included in the systematic review was an even smaller low-quality, randomized, double-blind, placebo-controlled crossover trial involving seven patients with

Parkinson's disease who had stable levodopa-induced dyskinesia present for 25–50 percent of the day (Sieradzan et al., 2001). Nabilone dosed at 0.03 mg/kg or a placebo was administered 12 hours and 1 hour before levodopa at a dose of 200 mg. The primary endpoint was total dyskinesia disability as measured using the Rush Dyskinesia Disability Scale.⁸ The median total dyskinesia score after treatment with levodopa and nabilone was 17 (range 11–25) compared to 22 (range 16–26) after levodopa and the placebo ($p < 0.05$). The anti-Parkinsonian actions of levodopa were not reduced by nabilone pretreatment. Although the authors stated that “nabilone significantly reduced total levodopa-induced dyskinesia compared with placebo” (Sieradzan et al., 2001, p. 2109), the fact that the results were generated by only seven patients receiving only two doses clearly reduces the ability to draw such an enthusiastic conclusion. Koppel concludes that oral cannabis extract “is probably ineffective for treating levodopa-induced dyskinesias” (Koppel et al., 2014, p. 1560).

Primary Literature

Cannabidiol capsules were evaluated in a randomized, double-blind, placebo-controlled trial conducted in 21 patients with Parkinson's disease (Chagas et al., 2014). The study was an exploratory trial to assess the effect of CBD in Parkinson's disease globally with the UPDRS and the Parkinson's Disease Questionnaire-39 (PDQ-39) used to assess overall functioning and well-being. Possible CBD adverse events were evaluated by a side effect rating scale. Baseline data were collected 1 week before commencing treatment with CBD at 75 mg/day or 300 mg/day or with a placebo, and the same assessments were repeated during the sixth and final week of the trial. No statistically significant differences were seen in the UPDRS between the three study arms. There was a statistically significant difference in the variation between baseline and final assessment in the overall PDQ-39 score between the placebo (6.50 ± 8.48) and CBD 300 mg/day (25.57 ± 16.30) ($p = 0.034$), which suggests that there might be a possible effect of CBD on improving quality of life.

An open-label observational study of 22 patients with Parkinson's disease attending a motor disorder clinic at a tertiary medical center collected data before and 30 minutes after patients smoked 0.5 grams of cannabis (Lotan et al., 2014). The instruments utilized included the UPDRS, the McGill Pain Scale, and a survey of subjective efficacy and adverse effects of cannabis. In addition, the effect of cannabis on motor symptoms was evaluated by two raters. The investigators found that the total

⁸ The Dyskinesia Disability Scale is a 0–4 scale (absent to most severe) measuring the severity of dyskinesia (Goetz et al., 1994).

motor symptoms score on the UPDRS improved from 33.1 (\pm 13.8) to 23.2 (\pm 10.5) ($p < 0.001$). Subcategories of the UPDRS that showed statistically significant improvement included tremor, rigidity, and bradykinesia. Pain and sleep were also reported to be improved after smoking cannabis. The results from this low-quality observational study prompted the investigators to propose that their findings should be confirmed in a larger, longer, randomized, double-blind, placebo-controlled trial.

Discussion of Findings

Small trials of oral cannabinoid preparations have demonstrated no benefit compared to a placebo in ameliorating the side effects of Parkinson's disease. A seven-patient trial of nabilone suggested that it improved the dyskinesia associated with levodopa therapy, but the sample size limits the interpretation of the data. An observational study of inhaled cannabis demonstrated improved outcomes, but the lack of a control group and the small sample size are limitations.

CONCLUSION 4-11 There is insufficient evidence that cannabinoids are an effective treatment for the motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia.

DYSTONIA

Dystonia is a disorder characterized by sustained or repetitive muscle contractions which result in abnormal fixed postures or twisting, repetitive movements (NINDS, 2016b). Idiopathic cervical dystonia is the most common cause of focal dystonia. Oral pharmacological agents are generally ineffective, with repeated injections of botulinum toxin being the most effective current therapy. The pathophysiologic mechanisms of dystonia are poorly understood, but, as in other hyperkinetic movement disorders, underactivity of the output regions of the basal ganglia may be involved. Stimulation of the cannabinoid receptors has been postulated as a way to reduce dystonia (Zadikoff et al., 2011). Anecdotal reports have suggested that cannabis may alleviate symptoms associated with dystonia (Uribe Roca et al., 2005). In a 1986 preliminary open pilot study in which five patients with dystonic movement disorders received cannabidiol, dose-related improvements were observed in all five patients (Consroe et al., 1986).

Are Cannabis or Cannabinoids an Effective Treatment for Dystonia?

Systematic Reviews

The American Academy of Neurology systematic review (Koppel et al., 2014) identified one study that examined the effect of dronabinol on cervical dystonia. The review described the study as being underpowered to detect any differences between dronabinol and the placebo. Overall, nine patients with cervical dystonia were randomized to receive dronabinol 15 mg daily or a placebo in an 8-week crossover trial (Zadikoff et al., 2011). The primary outcome measure was the change in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) part A subscore at the beginning and the end of each 3-week treatment phase. There was no statistically significant effect of dronabinol on the dystonia compared with the placebo as measured by the TWSTRS-A ($p = 0.24$).

Primary Literature

Fifteen patients with a clinical diagnosis of primary dystonia received a single dose of nabilone or placebo (0.03 mg/kg to the nearest whole milligram) on the study day (Fox et al., 2002). The primary outcome measure was the dystonia-movement scale portion of the Burke-Fahn-Marsden dystonia scale. Treatment with nabilone produced no significant reduction in the total dystonia movement scale score when compared with placebo ($p > 0.05$).

Discussion of Findings

Two small trials of dronabinol and nabilone failed to demonstrate a significant benefit of the cannabinoids in improving dystonia compared with placebo. Cannabis has not been studied in the treatment of dystonia.

CONCLUSION 4-12 There is insufficient evidence to support or refute the conclusion that nabilone and dronabinol are an effective treatment for dystonia.

DEMENTIA

Dementia is characterized by a decline in cognition that typically affects multiple cognitive domains such as memory, language, executive function, and perceptual motor function (NIH, 2013). Alzheimer's disease, vascular dementia, and Parkinson's disease with dementia are three prominent dementing disorders (NIA, n.d.). Behavioral and psychological symptoms, including agitation, aggression, and food refusal, are common

in the more advanced stages of dementia. These symptoms cause distress to the patient and caregivers and may precipitate the patient being placed in institutional care. Current treatments for dementia (e.g., cholinesterase inhibitors) have only modest effects, and treatments for behavioral disturbances such as antipsychotic medications have both modest benefits and substantial adverse effects (Krishnan et al., 2009).

CB₁ receptors are found throughout the central nervous system, and the endogenous cannabinoid system is thought to be important in the regulation of synaptic transmission (Baker et al., 2003), a process that is disordered in patients with dementia. Accumulating evidence suggests that cannabinoids have the potential for neuroprotective effects (Grundy, 2002; Hampson et al., 1998; Shen and Thayer, 1998). This developing understanding of the endogenous cannabinoid system, along with cannabinoids' anxiolytic and appetite-stimulating effects, provides a rationale for its study in patients with dementia.

Are Cannabis or Cannabinoids an Effective Treatment for the Symptoms Associated with Dementia?

Systematic Reviews

We identified two good-quality systematic reviews (Krishnan et al., 2009; van den Elsen et al., 2014) that evaluated cannabis for dementia. Both reviews identified the same two RCTs, which were synthesized qualitatively. A small randomized crossover trial (Volicer et al., 1997) evaluated dronabinol in 15 hospitalized patients with probable Alzheimer's disease who had behavior changes and were refusing food. Patients were randomized to dronabinol (2.5 mg twice daily) for 6 weeks and to a placebo for 6 weeks. Data in this trial with a high risk of bias were presented in such a way that they could not be abstracted for analysis by systematic review authors. The primary study authors reported: increased weight during the 12 weeks regardless of order of treatment (dronabinol, 7.0 [SD 1.5] pounds, and placebo, 4.6 [SD 1.3] pounds, during the first 6 weeks); decreased disturbed behavior during dronabinol treatment, an effect that persisted in patients treated first with dronabinol, then the placebo; decreased negative affect scores in both groups during the 12 weeks, more so when taking dronabinol than the placebo; and no serious adverse events attributed to dronabinol, although one patient suffered a seizure following the first dose. One other open-label pilot study (Walther et al., 2006), which evaluated six patients with severe dementia for the effects of dronabinol on nighttime agitation, did not meet eligibility criteria for the review by Krishnan et al. (2009).

Primary Literature

We identified one good-quality RCT that evaluated THC in 50 patients with Alzheimer’s disease, vascular or mixed dementia, and neuropsychiatric symptoms (van den Elsen et al., 2015). THC 1.5 mg given three times daily for 3 weeks did not improve overall neuropsychiatric symptoms, agitation, quality of life, or activities of daily living versus a placebo. Although the study recruited less than one-half of the planned sample, the authors estimated that there was only a 5 percent chance that enrolling more participants would have shown a clinically important effect on neuropsychiatric symptoms.

Discussion of Findings

The authors of the good-quality Cochrane systematic review concluded that the “review finds no evidence that cannabinoids are effective in the improvement of disturbed behavior in dementia or treatment of other symptoms of dementia” (Krishnan et al., 2009, p. 8). Subsequently, a larger good-quality RCT found no benefit from low-dose THC. We agree that the evidence is limited due to the small number of patients enrolled, limits in the study design and reporting, and inconsistent effects. The current limited evidence does not support a therapeutic effect of cannabinoids.

CONCLUSION 4-13 There is limited evidence that cannabinoids are ineffective treatments for improving the symptoms associated with dementia.

GLAUCOMA

Glaucoma is one of the leading causes of blindness within the United States (Mayo Clinic, 2015). This disorder is characterized as a group of eye conditions that can produce damage to the optic nerve and result in a loss of vision. This damage is often caused by abnormally high intraocular pressure (NEI, n.d.). Because high intraocular pressure is a known major risk factor that can be controlled (Prum et al., 2016, p. 52), most treatments have been designed to reduce it. Research suggests that cannabinoids may have potential as an effective treatment for reducing pressure in the eye (Tomida et al., 2007).

Are Cannabis or Cannabinoids an Effective Treatment for Glaucoma?

Systematic Reviews

We identified one good-quality systematic review (Whiting et al., 2015) that evaluated medical cannabis for the treatment of glaucoma. This review identified a single randomized crossover trial (six participants) in patients with glaucoma. The trial compared THC (5 mg oromucosal spray), cannabidiol (20 mg oromucosal spray), cannabidiol spray (40 mg oromucosal spray), and a placebo, examining intraocular pressure intermittently up until 12 hours after treatment. Elevated intraocular pressure is one of the diagnostic criteria for glaucoma, and lowering intraocular pressure is a goal of glaucoma treatments (Prum et al., 2016). The trial was evaluated as “unclear” risk of bias. No differences in intraocular pressure were found between placebo and cannabinoids.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for the symptoms of glaucoma and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

Lower intraocular pressure is a key target for glaucoma treatments. Non-randomized studies in healthy volunteers and glaucoma patients have shown short-term reductions in intraocular pressure with oral, topical eye drops, and intravenous cannabinoids, suggesting the potential for therapeutic benefit (IOM, 1999, pp. 174–175). A good-quality systemic review identified a single small trial that found no effect of two cannabinoids, given as an oromucosal spray, on intraocular pressure (Whiting et al., 2015). The quality of evidence for the finding of no effect is limited. However, to be effective, treatments targeting lower intraocular pressure must provide continual rather than transient reductions in intraocular pressure. To date, those studies showing positive effects have shown only short-term benefit on intraocular pressure (hours), suggesting a limited potential for cannabinoids in the treatment of glaucoma.

CONCLUSION 4-14 There is limited evidence that cannabinoids are an ineffective treatment for improving intraocular pressure associated with glaucoma.

TRAUMATIC BRAIN INJURY/INTRACRANIAL HEMORRHAGE

Traumatic brain injury (TBI) is an acquired brain injury that can result from a sudden or violent hit to the head (NINDS, 2016c). TBI accounts for about 30 percent of all injury deaths in the United States (CDC, 2016). Intracranial hemorrhage (ICH), bleeding that occurs inside the skull, is a common complication of TBI which is associated with a worse prognosis of the injury (Bullock, 2000; CDC, 2015). There is a small body of literature reporting the neuroprotective effects of cannabinoid analogues in preclinical studies of head injuries (Mechoulam et al., 2002) as well as in observational studies in humans (Di Napoli et al., 2016; Nguyen et al., 2014).

Are Cannabis or Cannabinoids an Effective Treatment or Prevention for Traumatic Brain Injury or Intracranial Hemorrhage?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that evaluated the efficacy of cannabinoids as a treatment or prevention for traumatic brain injury or intracranial hemorrhage.

Primary Literature

There were two fair- to high-quality observational studies found in the literature. One study (n = 446) examined the TBI presentation and outcomes among patients with and without a positive THC blood test (Nguyen et al., 2014). Patients who were positive for THC were more likely to survive the TBI than those who were negative for THC (OR, 0.224, 95% CI = 0.051–0.991). The authors used regression analysis to account for confounding variables (e.g., age, alcohol, Abbreviated Injury Score, Injury Severity Score, mechanism of injury, gender, and ethnicity). In the only other observational study that examined the association between cannabis use and brain outcomes, a study of intracranial hemorrhage patients (n = 725) found that individuals with a positive test of cannabis use demonstrated better primary outcome scores on the modified Rankin Scale⁹ (adjusted common OR, 0.544, 95% CI = 0.330–0.895) (Di Napoli et al., 2016). In their analysis, the authors adjusted for confounding variables that are known to be associated with worse ICH outcomes, including age, sex, Glasgow Coma Scale as continuous variables, and anticoagulant use.

⁹ The modified Rankin Scale is a clinical assessment tool commonly used to measure the degree of disability following a stroke. Outcome scores from the scale range from 0 (no symptoms) to 6 (death) (Di Napoli et al., 2016, p. 249).

Discussion of Findings

The two studies discussed above (Di Napoli et al., 2016; Nguyen et al., 2014) provide very modest evidence that cannabis use may improve outcomes after TBI or ICH. However, more conclusive observational studies or randomized controlled trials will be necessary before any conclusions can be drawn about the neuroprotective effect of cannabinoids in clinical populations.

CONCLUSION 4-15 There is limited evidence of a statistical association between cannabinoids and better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage.

ADDICTION

Drug addiction has been defined as a chronically relapsing disorder that is characterized by the compulsive desire to seek and use drugs with impaired control over substance use despite negative consequences (Prud'homme et al., 2015). The endocannabinoid system has been found to influence the acquisition and maintenance of drug-seeking behaviors, possibly through its role in reward and brain plasticity (Gardner, 2005; Heifets and Castillo, 2009). Furthermore, in laboratory settings orally administered dronabinol has been found to reduce cannabis withdrawal symptoms in cannabis users who were not seeking treatment to reduce cannabis use (Budney et al., 2007; Haney et al., 2004) and therefore may be expected to be useful as a substitute to assist to achieve and maintain abstinence of cannabis.

Are Cannabis or Cannabinoids an Effective Treatment for Achieving Abstinence from Addictive Substances?

Systematic Reviews

We identified two recent published reviews that examined randomized trials evaluating the effects of cannabis or cannabinoids on the use of addictive drugs, including cannabis: one systematic review by Marshall et al. (2014) and one comprehensive review by Prud'homme et al. (2015).¹⁰

The review by Marshall et al. (2014) is a high-quality systematic

¹⁰ Prud'homme (2015) is often categorized as a systematic review; however, the committee determined that the review lacks certain key elements of a systematic review, including a clearly stated research question, independent and duplicate data abstraction efforts, an assessment of the research quality and risk of bias, and a quantitative summary.

review of randomized and quasi-randomized trials assessing the efficacy of drug therapies specifically for cannabis dependence. They identified two trials examining THC: one published by Levin et al. (2011), examining dronabinol, and one published by Allsop et al. (2014), examining nabiximols.

The trial by Levin et al. (2011) was a randomized, placebo-controlled double-blind trial, which assigned cannabis-dependent adults to receive dronabinol ($n = 79$) or a placebo ($n = 77$) for 8 weeks, followed by a 2-week taper. Both groups received weekly individual therapy plus motivational enhancement therapy. Retention in the treatment program at the end of the maintenance phase was 77 percent in the dronabinol group and 61 percent in the placebo group (p -value for difference between groups = 0.02). Withdrawal symptoms declined more quickly in the dronabinol group than in the placebo group ($p = 0.02$). However, the primary outcome, the proportion of participants who achieved 2 consecutive weeks of abstinence at weeks 7 to 8, was 17.7 percent in the dronabinol group and 15.6 percent in the placebo group, which were not statistically significantly different from one another ($p = 0.69$).

The trial by Allsop et al. (2014) was randomized, placebo-controlled, and double-blind, and it enrolled adults seeking treatment for cannabis dependence. Subjects were patients who were hospitalized for 9 days and who received a 6-day regimen of nabiximols oromucosal spray ($n = 27$) or a matching placebo ($n = 24$) together with standardized psychosocial interventions. The primary outcome was a change in the Cannabis Withdrawal Scale, which is a 19-item scale that measures withdrawal symptom severity on an 11-point Likert scale for the previous 24 hours. Over the 6-day treatment period, subjects in the nabiximols group reported a mean 66 percent reduction from baseline in the cannabis withdrawal scale, while patients in the placebo group reported a mean increase in the cannabis withdrawal scale of 52 percent (p -value for between-group difference = 0.01). The median time between hospital discharge and relapse to cannabis use was 15 days (95% CI = 3.55–26.45) in the nabiximols group and 6 days (95% CI = 0–27.12) in the placebo group. The difference between these times was not statistically significant (p -value for between-group difference = 0.81).

Based on the Levin et al. (2011) and Allsop et al. (2014) trials, Marshall et al. (2014) concluded that there was moderate-quality evidence that users of THC preparations were more likely to complete treatment than those given a placebo (RR, 1.29, 95% CI = 1.08–1.55). However, the systematic review further concluded that, based on these two trials, the studied THC preparations were not associated with an increased likelihood of abstinence or a greater reduction in cannabis use than a placebo.

The review by Prud'homme et al. (2015) is a comprehensive review

that broadly examined evidence on the effects of cannabidiol on addictive behaviors. The only randomized trial assessing the role of cannabis in reducing the use of an addictive substance was published by Morgan et al. (2013). That study was a pilot placebo-controlled trial that randomized cigarette smokers who wished to quit smoking to receive 400 µg inhaled cannabidiol ($n = 12$) or inhaled placebo ($n = 12$) for 1 week. Participants were instructed to use the inhaler when they felt the urge to smoke. The reduction in the number of cigarettes smoked per week was higher in the cannabidiol group than in the placebo group, although the difference was not statistically significant ($p = 0.054$). Rates of abstinence were not reported.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for the reduction in use of addictive substances and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

Based on the systematic reviews, neither of the two trials evaluating the efficacy of a cannabinoid in achieving or sustaining abstinence from cannabis showed a statistically significant effect. However, given the limited number of studies and their small size, their findings do not definitively rule out the existence of an effect. The only study examining the efficacy of a cannabinoid in cigarette smoking cessation was a pilot study that did not examine rates of abstinence. Thus, its efficacy for smoking cessation has not been thoroughly evaluated.

CONCLUSION 4-16 There is no evidence to support or refute the conclusion that cannabinoids are an effective treatment for achieving abstinence in the use of addictive substances.

ANXIETY

Anxiety disorders share features of excessive fear and anxiety which induce psychological and physical symptoms that can cause significant distress or interfere with social, occupational, and other areas of functioning (APA, 2013). In a given year, an estimated 18 percent of the U.S. adult population will suffer from symptoms associated with an anxiety disorder (NIMH, n.d.). Given the role of the endocannabinoid system in mood

regulation, the committee decided to explore the relationship between anxiety and cannabis.

Are Cannabis or Cannabinoids an Effective Treatment for the Improvement of Anxiety Symptoms?

Systematic Reviews

The review by Whiting et al. (2015) was the most recent good-quality review. This review identified one randomized trial with a high risk of bias that compared a single 600 mg dose of cannabidiol to a placebo in 24 participants with generalized social anxiety disorder. Cannabidiol was associated with a greater improvement on the anxiety factor of a 100-point visual analogue mood scale (mean difference from baseline -16.52 , $p = 0.01$) compared with a placebo during a simulated public speaking test. Four other randomized controlled trials (232 participants) enrolled patients with chronic pain and reported on anxiety symptoms. The cannabinoids studied were: dronabinol, 10–20 mg daily; nabilone, maximum dose of 2 mg daily; and nabiximols, maximum dose of 4–48 sprays/day. Outcomes were assessed from 8 hours to 6 weeks after randomization; three of the four trials were judged to have a high risk of bias. These trials suggested greater short-term benefit with cannabinoids than a placebo on self-reported anxiety symptoms.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for the improvement of anxiety symptoms and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

There is limited evidence that cannabidiol improves anxiety symptoms, as assessed by a public speaking test, in patients with social anxiety disorder. These positive findings are limited by weaknesses in the study design (e.g., an inadequate description of randomization and allocation concealment), a single dose of CBD, and uncertain applicability to patients with other anxiety disorders. Limited evidence also suggests short-term benefits in patients with chronic pain and associated anxiety symptoms. In contrast, evidence from observational studies found moderate evidence that daily cannabis use is associated with increased anxiety symptoms

and heavy cannabis use is associated with social phobia disorder (see Chapter 12).

CONCLUSION 4-17 There is limited evidence that cannabidiol is an effective treatment for the improvement of anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders.

DEPRESSION

Depression is one of the nation's most common mental health disorders (ADAA, 2016). Across the many depressive disorders that exist (e.g., persistent depressive disorder, major depressive disorder, premenstrual dysphoric disorder) there are common symptomatic features of feelings of sadness, emptiness, or irritable mood, accompanied by somatic and cognitive changes that affect the individual's capacity to function (APA, 2013, p. 155). The endocannabinoid system is known to play a role in mood regulation (NIDA, 2015, p. 9); therefore, the committee decided to explore the association between cannabis use and depressive disorders or symptoms.

Are Cannabis or Cannabinoids an Effective Treatment to Reduce Depressive Symptoms?

Systematic Reviews

The review by Whiting et al. (2015) was the most recent good-quality review. No RCTs were identified that specifically evaluated cannabis in patients with a depressive disorder. Five RCTs (634 participants) enrolled patients for other conditions (chronic pain or multiple sclerosis with spasticity) and reported on depressive symptoms. Only one study reported depressive symptoms at baseline; symptoms were mild. Nabiximols ($n = 3$; maximum dose ranged from 4–48 doses/day), dronabinol (10 mg and 20 mg daily), and nabilone capsules (maximum of 8 mg) were compared to placebo; nabilone was also compared to dihydrocodeine. Outcomes were assessed from 8 hours to 9 weeks following randomization. Three of the five trials were judged to have a high risk of bias and the other two as unclear risk. Three studies (nabiximols, dronabinol) showed no effect using validated symptom scales. One study that evaluated three doses of nabiximols found increased depressive symptoms at the highest dose (11–14 sprays/day), but no difference compared to the placebo at lower doses. The comparison of nabilone to dihydrocodone showed no difference in depressive symptoms.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment to reduce depressive symptoms and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

Although patients report using cannabinoids for depression, our search for a good-quality systematic review did not identify any RCTs evaluating the effects of medical cannabis in patients with depressive disorders. Trials in patients with chronic pain or multiple sclerosis with uncertain baseline depressive symptoms did not show an effect. There are no trial data addressing the effects of cannabinoids for major depressive disorder.

In Chapter 12 (Mental Health), the committee reviews epidemiological evidence to examine the association between cannabis use and the development of depressive disorders as well as the impact of cannabis use on the disorder's course or symptoms.

CONCLUSION 4-18 There is limited evidence that nabiximols, dronabinol, and nabilone are ineffective treatments for the reduction of depressive symptoms in individuals with chronic pain or multiple sclerosis.

SLEEP DISORDERS

Sleep disorders can be classified into major groups that include insomnia, sleep-related breathing disorders, parasomnias, sleep-related movement disorders, and circadian rhythm sleep-wake disorders (Sateia, 2014). Fifty million to 70 million adults in the United States report having some type of sleep disorder (ASA, 2016). In 2010, insomnia generated 5.5 million office visits in the United States (Ford et al., 2014). There is some evidence to suggest that the endocannabinoid system may have a role in sleep. THC is associated in a dose-dependent manner with changes in slow-wave sleep, which is critical for learning and memory consolidation. Cannabis may also have effects on sleep latency, decreasing time to sleep onset at low doses and increasing time to sleep onset at higher doses (Garcia and Salloum, 2015). Thus, cannabinoids could have a role in treating sleep disorders.

Are Cannabis or Cannabinoids an Effective Treatment for Improving Sleep Outcomes?

Systematic Reviews

The review by Whiting et al. (2015) was the most recent good-quality review. Two RCTs (54 participants) evaluated cannabinoids (nabilone, dronabinol) for the treatment of sleep problems. A trial deemed to have a high risk of bias conducted in 22 patients with obstructive sleep apnea showed a greater benefit of dronabinol (maximum dose of 10 mg daily) than with a placebo on sleep apnea/hypopnea index (mean difference from baseline -19.64 , $p = 0.02$) at 3 weeks follow-up. A crossover trial deemed to have a low risk of bias in 32 patients with fibromyalgia found improvements for nabilone 0.5 mg daily compared with 10 mg amitriptyline in insomnia (mean difference from baseline, -3.25 , 95% CI = -5.26 to -1.24) and greater sleep restfulness (mean difference from baseline, 0.48 , 95% CI = 0.01 – 0.95) at 2 weeks follow-up. Although the antidepressant amitriptyline is an established treatment for fibromyalgia, it is not FDA approved for insomnia, and its use is limited by adverse effects.

Nineteen trials (3,231 participants) enrolled patients with other conditions (chronic pain or multiple sclerosis) and reported on sleep outcomes. Nabiximols (13 studies), THC/CBD capsules (2 studies), smoked THC (2 studies), and dronabinol or nabilone were compared to a placebo. Sleep outcomes were assessed at 2–15 weeks after randomization. Eleven of the 19 trials were judged to have a high risk of bias, 6 had an uncertain risk of bias, and the other 2 were judged to have a low risk of bias. The meta-analysis found greater improvements with cannabinoids in sleep quality among 8 trials (weighted mean difference [WMD], -0.58 , 95% CI = -0.87 to -0.29) and sleep disturbance among 3 trials (WMD, -0.26 , 95% CI = -0.52 to 0.00). These improvements in sleep quality and sleep disturbance were rated on a 10-point scale and would be considered small improvements. The summary estimate showing benefit was based primarily on studies of nabiximols.

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment to improve sleep outcomes and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

A high-quality systematic review found moderate evidence suggesting that cannabinoids (primarily nabiximols) improve short-term sleep outcomes in patients with sleep disturbance associated with obstructive sleep apnea, fibromyalgia, chronic pain, or multiple sclerosis. However, the single study using an active comparator used a drug (amitriptyline) that is considered second-line treatment due to the availability of newer, more effective treatments that have fewer adverse effects. The committee did not identify any clinical trials that evaluated the effects of cannabinoids in patients with primary chronic insomnia.

CONCLUSION 4-19 There is moderate evidence that cannabinoids, primarily nabiximols, are an effective treatment to improve short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis.

POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder (PTSD) falls within the broader trauma- and stressor-related disorders categorized by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V). The diagnostic criteria of PTSD include an exposure to a traumatic event (e.g., the threat of death, serious injury, or sexual violence) and exhibiting psychological distress symptoms that occur as a result of that exposure (e.g., intrusion symptoms, such as distressing memories; avoidance of stimuli that are associated with the traumatic event; negative alterations in mood and cognition; alterations in arousal and reactivity associated with the traumatic event; functional impairment) (APA, 2013, pp. 271–272). Given the known psychoactive effects of cannabis, the committee decided to explore the association between PTSD and cannabis use.

**Are Cannabis or Cannabinoids an Effective
Treatment for PTSD Symptoms?**

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on medical cannabis as an effective treatment for PTSD symptoms.

Primary Literature

We identified a fair-quality double-blind, randomized crossover trial (Jetly et al., 2015) conducted with Canadian male military personnel with trauma-related nightmares despite standard treatments for PTSD. Ten participants were randomized to either nabilone 0.5 mg that was titrated to a daily maximum of 3.0 mg or else to a placebo for 7 weeks. Following a 2-week washout period, subjects were then treated with the other study treatment and followed for an additional 7 weeks. Effects on sleep, nightmares, and global clinical state were assessed by the investigators; sleep time and general well-being were self-reported. Nightmares, global clinical state, and general well-being were improved more with nabilone treatment than with the placebo treatment ($p < 0.05$). There was no effect on sleep quality and quantity. Global clinical state was rated as very much improved or much improved for 7 of 10 subjects in the nabilone treatment period and 2 of 10 subjects in the placebo treatment period.

Discussion of Findings

A single, small crossover trial suggests potential benefit from the pharmaceutical cannabinoid nabilone. This limited evidence is most applicable to male veterans and contrasts with non-randomized studies showing limited evidence of a statistical association between cannabis use (*plant derived forms*) and *increased* severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (see Chapter 12). A search of the grey literature identified several recently initiated randomized controlled trials examining the harms and benefits of marijuana for PTSD.¹¹ One trial examines the effects of four different types of cannabis with varying THC and CBD content on PTSD symptoms in 76 veterans (Bonn-Miller, 2016). Another trial is a Canadian study that evaluates different formulations of THC and CBD in 42 adults with PTSD (Eades, 2016). If these trials are successfully completed, they will add substantially to the knowledge base, expanding the range of cannabinoids evaluated and the opportunity to examine the consistency of effects across studies.

CONCLUSION 4-20 There is limited evidence (a single, small fair-quality trial) that nabilone is effective for improving symptoms of posttraumatic stress disorder.

¹¹ ClinicalTrials.gov: NCT02102230, NCT02874898, NCT02517424, NCT02759185.

SCHIZOPHRENIA AND OTHER PSYCHOSES

Schizophrenia spectrum disorders and other psychotic disorders are mental health disorders characterized by three different classes of symptoms: positive symptoms (e.g., delusions, hallucinations, or disorganized or abnormal motor behavior), negative symptoms (e.g., diminished emotional expression, lack of interest or motivation to engage in social settings, speech disturbance, or anhedonia), and impaired cognition (e.g., disorganized thinking) (APA, 2013, p. 87; NIMH, 2015). Evidence suggests that the prevalence of cannabis use among people with schizophrenia is generally higher than among the general population (McLoughlin et al., 2014). In most of the studies reviewed below, schizophrenia, schizophreniform disorder, schizoaffective disorder, and psychotic disorders are used as aggregate endpoints.

Are Cannabis or Cannabinoids an Effective Treatment for the Mental Health Outcomes of Patients with Schizophrenia or Other Psychoses?

Systematic Reviews

Two good-quality reviews (McLoughlin et al., 2014; Whiting et al., 2015) evaluated cannabinoids for the treatment of psychosis. We focus on the good-quality review by Whiting et al. (2015) as it is more current. Two RCTs with high risk of bias (71 total participants with schizophrenia or schizophreniform psychosis) compared cannabidiol to the atypical antipsychotic amisulpride or a placebo. One trial reported no difference on mental health between CBD (maximum dose 800 mg/day) and amisulpride (maximum dose 800 mg/day) at 4 weeks (brief psychiatric rating scale mean difference, -0.10 , 95% CI = -9.20 – 8.90) or on mood (positive and negative syndrome scale mean difference, 1.0 ; 95% CI = -12.6 – 14.6). A crossover trial showed no difference in effect on mood between CBD (maximum dose 600 mg/day) and placebo (positive and negative symptom scale mean difference, 1 , 95% CI = -12.60 – 14.60 ; scale range 30–210).

Primary Literature

The committee did not identify any good-quality primary literature that reported on medical cannabis as an effective treatment for the mental health outcomes of patients with schizophrenia or other psychoses and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

Good-quality systematic reviews identified only two small, unclear-to-high-risk-of-bias trials evaluating cannabinoids for the treatment of schizophrenia. These studies provide only limited evidence due to the risk of bias, the short-term follow-up, and the evaluation of a single cannabinoid. Furthermore, the larger trial was designed to detect a moderate benefit of cannabidiol compared to the antipsychotic amisulpride, but it enrolled only 60 percent of the planned sample. Thus, it did not have the statistical power to detect small or moderate differences between CBD and amisulpride. Overall, the evidence is insufficient to determine if cannabidiol is an effective treatment for individuals with schizophrenia or schizopreniform psychosis.

In Chapter 12, the committee reviews epidemiological evidence to examine the association between cannabis use and the development of schizophrenia and other psychoses, as well as the impact of cannabis use on the disorder's course or symptoms.

CONCLUSION 4-21 There is insufficient evidence to support or refute the conclusion that cannabidiol is an effective treatment for the mental health outcomes in individuals with schizophrenia or schizopreniform psychosis.

RESEARCH GAPS

In reviewing the research evidence described above, the committee has identified that research gaps exist concerning the effectiveness of cannabidiol or cannabidiol-enriched cannabis in treating the following:

- cancer in general
- treating chemotherapy-induced nausea and vomiting
- symptoms of irritable bowel syndrome
- epilepsy
- spasticity due to paraplegia from spinal cord injury
- symptoms associated with amyotrophic lateral sclerosis
- motor function and cognitive performance associated with Huntington's Disease
- motor system symptoms associated with Parkinson's disease or levodopa-induced dyskinesia
- achieving abstinence or reduction in the use of addictive substances, including cannabis itself
- sleep outcomes in individuals with primary chronic insomnia
- posttraumatic stress disorder symptoms

- mental health outcomes in individuals with schizophrenia or schizophreniform psychosis
- cannabidiol short-term relief from anxiety symptoms

SUMMARY

This chapter outlines the committee's efforts to review the current evidence base for the potential efficacy of cannabis or cannabinoids on prioritized health conditions. The health conditions reviewed in this chapter include chronic pain, cancer, chemotherapy-induced nausea and vomiting, anorexia and weight loss associated with HIV, irritable bowel syndrome, epilepsy, spasticity, Tourette syndrome, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, dystonia, dementia, glaucoma, traumatic brain injury, addiction, anxiety, depression, sleep disorders, posttraumatic stress disorder, and schizophrenia and other psychoses. The committee has formed a number of research conclusions related to these health endpoints; however, it is important that the chapter conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections above. See Box 4-1 for a summary list of the chapter's conclusions.

We found conclusive or substantial evidence (ranging in modest to moderate effect) for benefit from cannabis or cannabinoids for chronic pain, chemotherapy-induced nausea and vomiting, and patient-reported symptoms of spasticity associated with multiple sclerosis. For chemotherapy-induced nausea and vomiting and spasticity associated with multiple sclerosis, the primary route of administration examined was the oral route. For chronic pain, most studies examined oral cannabis extract, although some examined smoked or vaporized cannabis. It is unknown whether and to what degree the results of these studies can be generalized to other products and routes of administration. For many of the other conditions discussed above, there is insufficient or no evidence upon which to base conclusions about therapeutic effects. The potential efficacy of cannabinoids for several of these conditions, such as epilepsy and posttraumatic stress disorder, should be prioritized, given the substantial number of persons using cannabis for those conditions (Cogle et al., 2011; Massot-Tarrús and McLachlan, 2016). As identified in the chapter's Discussion of Findings sections, there are common themes in the type of study limitations found in this evidence base. The most common are limitations in the study design (e.g., a lack of appropriate control groups, a lack of long-term follow-ups), small sample sizes, and research gaps in examining the potential therapeutic benefits of different forms of cannabis (e.g., cannabis plant). These limitations highlight the need for substantial research to provide comprehensive and conclusive evidence on the therapeutic effects of cannabis and cannabinoids.

BOX 4-1 Summary of Chapter Conclusions*

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults (cannabis) (4-1)
- As antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)

There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols) (4-19)

There is limited evidence that cannabis or cannabinoids are effective for:

- Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids) (4-4a)
- Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)
- Improving symptoms of Tourette syndrome (THC capsules) (4-8)
- Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol) (4-17)
- Improving symptoms of posttraumatic stress disorder (nabilone; a single, small fair-quality trial) (4-20)

There is limited evidence of a statistical association between cannabinoids and:

- Better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage (4-15)

REFERENCES

- Abel, E. L. 1975. Cannabis: Effects on hunger and thirst. *Behavioral Biology* 15(3):255–281.
- Abrams, D. I., C. A. Jay, S. B. Shade, H. Vizoso, H. Reda, S. Press, M. E. Kelly, M. C. Rowbotham, and K. L. Petersen. 2007. Cannabis in painful HIV-associated sensory neuropathy: A randomized placebo-controlled trial. *Neurology* 68(7):515–521.
- ADAA (Anxiety and Depression Association of America). 2016. Depression. <https://www.adaa.org/understanding-anxiety/depression> (accessed November 17, 2016).

There is limited evidence that cannabis or cannabinoids are *ineffective* for:

- Improving symptoms associated with dementia (cannabinoids) (4-13)
- Improving intraocular pressure associated with glaucoma (cannabinoids) (4-14)
- Reducing depressive symptoms in individuals with chronic pain or multiple sclerosis (nabiximols, dronabinol, and nabilone) (4-18)

There is no or insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are an effective treatment for:

- Cancers, including glioma (cannabinoids) (4-2)
- Cancer-associated anorexia cachexia syndrome and anorexia nervosa (cannabinoids) (4-4b)
- Symptoms of irritable bowel syndrome (dronabinol) (4-5)
- Epilepsy (cannabinoids) (4-6)
- Spasticity in patients with paralysis due to spinal cord injury (cannabinoids) (4-7b)
- Symptoms associated with amyotrophic lateral sclerosis (cannabinoids) (4-9)
- Chorea and certain neuropsychiatric symptoms associated with Huntington's disease (oral cannabinoids) (4-10)
- Motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia (cannabinoids) (4-11)
- Dystonia (nabilone and dronabinol) (4-12)
- Achieving abstinence in the use of addictive substances (cannabinoids) (4-16)
- Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis (cannabidiol) (4-21)

* Numbers in parentheses correspond to chapter conclusion numbers.

Allsop, D. J., J. Copeland, N. Lintzeris, A. J. Dunlop, M. Montebello, C. Sadler, G. R. Rivas, R. M. Holland, P. Muhleisen, M. M. Norberg, J. Booth, and I. S. McGregor. 2014. Nabiximols as an agonist replacement therapy during cannabis withdrawal: A randomized clinical trial. *JAMA Psychiatry* 71(3):281–291.

Andreae, M. H., G. M. Carter, N. Shaparin, K. Suslov, R. J. Ellis, M. A. Ware, D. I. Abrams, H. Prasad, B. Wilsey, D. Indyk, M. Johnson, and H. S. Sacks. 2015. Inhaled cannabis for chronic neuropathic pain: A meta-analysis of individual patient data. *Journal of Pain* 16(12):1121–1232.

- Andries, A., J. Frystyk, A. Flyvbjerg, and R. K. Støving. 2014. Dronabinol in severe, enduring anorexia nervosa: A randomized controlled trial. *International Journal of Eating Disorders* 47(1):18–23.
- APA (American Psychiatric Association). 2013. *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.
- Armstrong, M. J., and J. M. Miyasaki. 2012. Evidence-based guideline: Pharmacologic treatment of chorea in Huntington disease: Report of the guideline development subcommittee of the American Academy of Neurology. *Neurology* 79(6):597–603.
- ASA (American Sleep Association). 2016. Sleep and sleep disorder statistics. <https://www.sleepassociation.org/sleep/sleep-statistics> (accessed October 25, 2016).
- Ashworth, B. 1964. Preliminary trial of carisoprodol in multiple sclerosis. *The Practitioner* 192:540–542.
- Baker, D., G. Pryce, G. Giovannoni, and A. J. Thompson. 2003. The therapeutic potential of cannabis. *The Lancet Neurology* 2:291–298.
- Belendiuk, K. A., L. L. Baldini, and M. O. Bonn-Miller. 2015. Narrative review of the safety and efficacy of marijuana for the treatment of commonly state-approved medical and psychiatric disorders. *Addiction Science & Clinical Practice* 10:10.
- Boehnke, K. F., E. Litinas, and D. J. Clauw. 2016. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. *Journal of Pain* 17(6):739–744.
- Bonn-Miller, M. 2016. Study of four different potencies of smoked marijuana in 76 veterans with chronic, treatment-resistant PTSD. ClinicalTrials.gov. Bethesda, MD: National Library of Medicine. <https://clinicaltrials.gov/ct2/show/NCT02759185> (accessed September 28, 2016).
- Bradford, A. C., and W. D. Bradford. 2016. Medical marijuana laws reduce prescription medication use in Medicare part D. *Health Affairs* 35(7):1230–1236.
- Budney, A. J., R. G. Vandrey, J. R. Hughes, B. A. Moore, and B. Bahrenburg. 2007. Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. *Drug and Alcohol Dependence* 86(1):22–29.
- Bullock, R., R. Chesnut, G. L. Clifton, J. Ghajar, D. W. Marion, R. K. Narayan, D. W. Newell, L. H. Pitts, M. J. Rosner, B. C. Walters, and J. E. Wilberger. 2000. Management and prognosis of severe traumatic brain injury. *Journal of Neurotrauma* 17:451–627.
- Canavan, C., J. West, and T. Card. 2014. The epidemiology of irritable bowel syndrome. *Clinical Epidemiology* 6:71–80.
- Carroll, C. B., P. G. Bain, L. Teare, X. Liu, C. Joint, C. Wroath, S. G. Parkin, P. Fox, D. Wright, J. Hobart, and J. P. Zajicek. 2004. Cannabis for dyskinesia in Parkinson disease: A randomized double-blind crossover study. *Neurology* 63(7):1245–1250.
- CDC (Centers for Disease Control and Prevention). 2015. Bleeding disorders glossary. <https://www.cdc.gov/ncbddd/hemophilia/communitycounts/glossary.html> (accessed November 17, 2016).
- CDC. 2016. TBI: Get the facts. http://www.cdc.gov/traumaticbraininjury/get_the_facts.html (accessed November 17, 2016).
- CDPHE (Colorado Department of Public Health and Environment). 2016. 2016 medical marijuana registry statistics. <https://www.colorado.gov/pacific/cdphe/2016-medical-marijuana-registry-statistics> (accessed October 28, 2016).
- Chagas, M. H. N., A. W. Zuardi, V. Tumas, M. A. Pena-Pereira, E. T. Sobreira, M. M. Bergamaschi, A. C. Dos Santos, A. L. Teixeira, J. E. C. Hallak, and J. A. S. Crippa. 2014. Effects of cannabidiol in the treatment of patients with Parkinson's disease: An exploratory double-blind trial. *Journal of Psychopharmacology* 28(11):1088–1092.

- Colorado DOR (Department of Revenue). 2016. MED 2015 Annual Update. Denver: Colorado Department of Revenue. https://www.colorado.gov/pacific/sites/default/files/2015%20Annual%20Update%20FINAL%2009262016_1.pdf (accessed December 7, 2016).
- Consroe, P., R. Sandyk, and S. Sinder. 1986. Open label evaluation of cannabidiol in dystonic movement disorders. *International Journal of Neuroscience* 30(4):277–282.
- Consroe, P., J. Laguna, J. Allender, S. Snider, L. Stern, R. Sandyk, K. Kennedy, and K. Schram. 1991. Controlled clinical trial of cannabidiol in Huntington’s disease. *Pharmacology, Biochemistry, and Behavior* 40(3):701–708.
- Cougle, J. R., M. O. Bonn-Miller, A. A. Vujanovic, M. J. Zvolensky, and K. A. Hawkins. 2011. Posttraumatic stress disorder and cannabis use in a nationally representative sample. *Psychology of Addictive Behaviors* 25(3):554–558.
- Curtis, A., I. Mitchell, S. Patel, N. Ives, and H. Rickards. 2009. A pilot study using nabilone for symptomatic treatment in Huntington’s disease. *Movement Disorders* 24(15):2254–2259.
- Devinsky, O., M. R. Cilio, H. Cross, J. Fernandez-Ruiz, J. French, C. Hill, R. Katz, V. Di Marzo, D. Jutras-Aswad, W. G. Notcutt, J. Martinez-Orgado, P. J. Robson, B. G. Rohrback, E. Thiele, B. Whalley, and D. Friedman. 2014. Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia* 55(6):791–802.
- Devinsky, O., E. Marsh, D. Friedman, E. Thiele, L. Laux, J. Sullivan, I. Miller, R. Flamini, A. Wilfong, F. Filloux, M. Wong, N. Tilton, P. Bruno, J. Bluvstein, J. Hedlund, R. Kamens, J. Maclean, S. Nangia, N. S. Singhal, C. A. Wilson, A. Patel, and M. R. Cilio. 2016. Cannabidiol in patients with treatment-resistant epilepsy: An open-label interventional trial. *The Lancet Neurology* 15(3):270–278.
- Di Napoli, M., A. M. Zha, D. A. Godoy, L. Masotti, F. H. Schreuder, A. Popa-Wagner, and R. Behrouz. 2016. Prior cannabis use is associated with outcome after intracerebral hemorrhage. *Cerebrovascular Disease* 41(5–6):248–255.
- Eades, J. 2016. Evaluating safety and efficacy of cannabis in participants with chronic post-traumatic stress disorder. ClinicalTrials.gov. Bethesda, MD: National Library of Medicine. <https://clinicaltrials.gov/ct2/show/NCT02517424> (accessed September 28, 2016).
- Esfandyari, T., M. Camilleri, I. Ferber, D. Burton, K. Baxter, and A. R. Zinsmeister. 2006. Effect of a cannabinoid agonist on gastrointestinal transit and postprandial satiation in healthy human subjects: A randomized, placebo-controlled study. *Neurogastroenterology & Motility* 18(9):831–838.
- Fitzcharles, M. A., P. A. Ste-Marie, W. Hauser, D. J. Clauw, S. Jamal, J. Karsh, T. Landry, S. LeClercq, J. J. McDougall, Y. Shir, K. Shojania, and Z. Walsh. 2016. Efficacy, tolerability, and safety of cannabinoid treatments in the rheumatic diseases: A systematic review of randomized controlled trials. *Arthritis Care and Research* 68(5):681–688.
- Foltin, R. W., M. W. Fischman, and M. F. Byrne. 1988. Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. *Appetite* 11(1):1–14.
- Ford, E. S., A. G. Wheaton, T. J. Cunningham, W. H. Giles, D. P. Chapman, and J. B. Croft. 2014. Trends in outpatient visits for insomnia, sleep apnea, and prescriptions for sleep medications among US adults: Findings from the National Ambulatory Medical Care survey 1999–2010. *Sleep* 37(8):1283–1293.
- Fox, S. H., M. Kellett, A. P. Moore, A. R. Crossman, and J. M. Brotchie. 2002. Randomised, double-blind, placebo-controlled trial to assess the potential of cannabinoid receptor stimulation in the treatment of dystonia. *Movement Disorders* 17(1):145–149.
- Garcia, A. N., and I. M. Salloum. 2015. Polysomnographic sleep disturbances in nicotine, caffeine, alcohol, cocaine, opioid, and cannabis use: A focused review. *American Journal of Addiction* 24(7):590–598.
- Gardner, E. L. 2005. Endocannabinoid signaling system and brain reward: Emphasis on dopamine. *Pharmacology, Biochemistry & Behavior* 81(2):263–284.

- Gelinas, D., R. G. Miller, and M. Abood. 2002. A pilot study of safety and tolerability of delta 9-THC (Marinol) treatment for ALS. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders* 3(Suppl 2):23–24.
- Gloss, D. S., and B. Vickrey. 2014. Cannabinoids for epilepsy. *Cochrane Database of Systematic Reviews* 3:CD009270.
- Goetz, C. G., G. T. Stebbins, H. M. Shale, A. E. Lang, D. A. Chernik, T. A. Chmura, J. E. Ahlskog, and E. E. Dorflinger. 1994. Utility of an objective dyskinesia rating scale for Parkinson's disease: Inter- and intrarater reliability assessment. *Movement Disorders* 9(4):390–394.
- Grotenhermen, F., and K. Müller-Vahl. 2012. The therapeutic potential of cannabis and cannabinoids. *Deutsches Ärzteblatt International* 109(29-30):495–501.
- Grundy, R. I. 2002. The therapeutic potential of the cannabinoids in neuroprotection. *Expert Opinion on Investigational Drugs* 11:1365–1374.
- GW Pharmaceuticals. 2016. Prescriber information. <http://dev-gwpharma.pantheonsite.io/products-pipeline/sativex/prescriber-information-full> (accessed November 15, 2016).
- Hampson, A. J., M. Grimaldi, J. Axelrod, and D. Wink. 1998. Cannabidiol and delta-9-tetrahydrocannabinol are neuroprotective antioxidants. *Proceedings of the National Academy of Sciences of the United States of America* 95:8268–8273.
- Haney, M., C. L. Hart, S. K. Vosburg, J. Nasser, A. Bennett, C. Zubarán, and R. W. Foltin. 2004. Marijuana withdrawal in humans: Effects of oral THC or divalproex. *Neuropsychopharmacology* 29(1):158–170.
- Heifets, B. D., and P. E. Castillo. 2009. Endocannabinoid signaling and long-term synaptic plasticity. *Annual Review of Physiology* 71:283–306.
- Hemming, M., and P. M. Yellowlees. 1993. Effective treatment of Tourette's syndrome with marijuana. *Journal of Psychopharmacology* 7:389–391.
- Ilgen, M. A., K. Bohnert, F. Kleinberg, M. Jannausch, A. S. Bohnert, M. Walton, and F. C. Blow. 2013. Characteristics of adults seeking medical marijuana certification. *Drug and Alcohol Dependence* 132(3):654–659.
- IOM (Institute of Medicine). 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC: National Academy Press.
- Jatoi, A., H. E. Windschitl, C. L. Loprinzi, J. A. Sloan, S. R. Dakhil, J. A. Mailliard, S. Pundaleeka, C. G. Kardinal, T. R. Fitch, J. E. Krook, P. J. Novotny, and B. Christensen. 2002. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: A North Central Cancer Treatment Group study. *Journal of Clinical Oncology* 20(2):567–573.
- Jetly, R., A. Heber, G. Fraser, and D. Boisvert. 2015. The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study. *Psychoneuroendocrinology* 51:585–588.
- Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.
- Krishnan, S., R. Cairns, and R. Howard. 2009. Cannabinoids for the treatment of dementia. *Cochrane Database of Systematic Reviews* (2):CD007204.
- Leocani, L., A. Nuara, E. Houdayer, I. Schiavetti, U. Del Carro, S. Amadio, L. Straffi, P. Rossi, V. Martinelli, C. Vila, M. P. Sormani, and G. Comi. 2015. Sativex® and clinical-neurophysiological measures of spasticity in progressive multiple sclerosis. *Journal of Neurology* 262(11):2520–2527.
- Levin, F. R., J. J. Mairani, D. J. Brooks, M. Pavlicova, W. Cheng, and E. V. Nunes. 2011. Dronabinol for the treatment of cannabis dependence: A randomized, double-blind, placebo-controlled trial. *Drug and Alcohol Dependence* 116(1–3):142–150.

- Light, M. K., A. Orens, B. Lewandowski, and T. Pickton. 2014. Market size and demand for marijuana in Colorado. *The Marijuana Policy Group*. <https://www.colorado.gov/pacific/sites/default/files/Market%20Size%20and%20Demand%20Study,%20July%209,%202014%5B1%5D.pdf> (accessed November 17, 2016).
- Lotan, I., T. A. Treves, Y. Roditi, and R. Djaldetti. 2014. Cannabis (medical marijuana) treatment for motor and non-motor symptoms of Parkinson disease: An open-label observational study. *Clinical Neuropharmacology* 37(2):41–44.
- Lutge, E. E., A. Gray, and N. Siegfried. 2013. The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. *Cochrane Database of Systematic Reviews* (4):CD005175.
- Marshall, K., L. Gowing, R. Ali, and B. Le Foll. 2014. Pharmacotherapies for cannabis dependence. *Cochrane Database of Systematic Reviews* 12:CD008940.
- Massot-Tarrús, A., and R. S. McLachlan. 2016. Marijuana use in adults admitted to a Canadian epilepsy monitoring unit. *Epilepsy & Behavior* 63:73–78.
- Mayo Clinic. 2015. Glaucoma. <http://www.mayoclinic.org/diseases-conditions/glaucoma/basics/definition/con-20024042> (accessed December 1, 2016).
- McLoughlin, B. C., J. A. Pushpa-Rajah, D. Gillies, J. Rathbone, H. Variend, E. Kalakouti, and K. Kyprianou. 2014. Cannabis and schizophrenia. *Cochrane Database of Systematic Reviews* (10):CD004837.
- Mechoulam, R., M. Spatz, and E. Shohami. 2002. Endocannabinoids and neuroprotection. *Science's STKE* (129):re5.
- Meiri, E., H. Jhangiani, J. J. Vredenburgh, L. M. Barbato, F. J. Carter, H. M. Yang, and V. Baranowski. 2007. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. *Current Medical Research and Opinion* 23(3):533–543.
- Mohanraj, R., and M. J. Brodie. 2006. Diagnosing refractory epilepsy: Response to sequential treatment schedules. *European Journal of Neurology* 13(3):277–282.
- Morgan, C. J. A., R. K. Das, A. Joye, H. V. Curran, and S. K. Kamboj. 2013. Cannabidiol reduces cigarette consumption in tobacco smokers: Preliminary findings. *Addictive Behaviors* 38(9):2433–2436.
- Müller-Vahl, K. R., A. Koblenz, M. Jöbges, H. Kolbe, H. M. Emrich, and U. Schneider. 2001. Influence of treatment of Tourette syndrome with Δ^9 -tetrahydrocannabinol (Δ^9 -THC) on neuropsychological performance. *Pharmacopsychiatry* 34(1):19–24.
- Müller-Vahl, K. R., U. Schneider, A. Koblenz, M. Jöbges, H. Kolbe, T. Daldrup, and H. M. Emrich. 2002. Treatment of Tourette's syndrome with Δ^9 -tetrahydrocannabinol (THC): A randomized crossover trial. *Pharmacopsychiatry* 35(2):57–61.
- Müller-Vahl, K. R., H. Prevedel, K. Theloe, H. Kolbe, H. M. Emrich, and U. Schneider. 2003a. Treatment of Tourette syndrome with delta-9-tetrahydrocannabinol (Δ^9 -THC): No influence on neuropsychological performance. *Neuropsychopharmacology* 28(2):384–388.
- Müller-Vahl, K. R., U. Schneider, H. Prevedel, K. Theloe, H. Kolbe, T. Daldrup, and H. M. Emrich. 2003b. Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: A 6-week randomized trial. *Journal of Clinical Psychiatry* 64(4):459–465.
- NCI (National Cancer Institute). 2015. What is cancer? <https://www.cancer.gov/about-cancer/understanding/what-is-cancer> (accessed November 16, 2016).
- NCI. 2016. Cancer statistics. <https://www.cancer.gov/about-cancer/understanding/statistics> (accessed October 28, 2016).
- NCSL (National Conference of State Legislatures). 2016. State medical marijuana laws. <http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx> (accessed November 17, 2016).
- NEI (National Eye Institute). n.d. What you should know. <https://nei.nih.gov/glaucoma/content/english/know> (accessed November 17, 2016).

- Nguyen, B., D. Kim, S. Bricker, F. Bongard, A. Neville, B. Putnam, J. Smith, and D. Plurad. 2014. Effects of marijuana use on outcomes in traumatic brain injury. *American Surgeon* 80(10):979–983.
- NIA (National Institute on Aging). n.d. About Alzheimer’s disease: Other dementias. <https://www.nia.nih.gov/alzheimers/topics/other-dementias> (accessed December 22, 2016).
- NIDA (National Institute on Drug Abuse). 2015. Research reports: Marijuana. https://www.drugabuse.gov/sites/default/files/mjrrs_4_15.pdf (accessed December 8, 2016).
- NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases). 2015. Definition and facts for irritable bowel syndrome. www.niddk.nih.gov/health-information/health-topics/digestive-diseases/irritable-bowel-syndrome/pages/definition-facts.aspx (accessed October 18, 2016).
- NIH (National Institutes of Health). 2013. The dementias: Hope through research. <file:///C:/Users/MMasiello/Downloads/the-dementias-hope-through-research.pdf> (accessed December 28, 2016).
- NIMH (National Institute of Mental Health). 2015. Schizophrenia. <https://www.nimh.nih.gov/health/publications/schizophrenia-booklet-12-2015/index.shtml> (accessed October 28, 2016).
- NIMH. n.d. Any mental illness (AMI) among U.S. adults. <https://www.nimh.nih.gov/health/statistics/prevalence/any-mental-illness-ami-among-us-adults.shtml> (accessed November 17, 2016).
- NINDS (National Institute of Neurological Disorders and Stroke). 2014. Tourette syndrome fact sheet. http://www.ninds.nih.gov/disorders/tourette/detail_tourette.htm (accessed December 2, 2016).
- NINDS. 2015. Parkinson’s disease: Challenges, progress, and promise. <https://catalog.ninds.nih.gov/pubstatic//15-5595/15-5595.pdf> (accessed December 28, 2016).
- NINDS. 2016a. The epilepsies and seizures: Hope through research. http://www.ninds.nih.gov/disorders/epilepsy/detail_epilepsy.htm (accessed November 16, 2016).
- NINDS. 2016b. Dystonias fact sheet. http://www.ninds.nih.gov/disorders/dystonias/detail_dystonias.htm (accessed November 18, 2016).
- NINDS. 2016c. Traumatic brain injury: Hope through research. http://www.ninds.nih.gov/disorders/tbi/detail_tbi.htm (accessed November 16, 2016).
- OHA (Oregon Health Authority). 2016. Oregon medical marijuana program statistics. <https://public.health.oregon.gov/DiseasesConditions/ChronicDisease/MedicalMarijuanaProgram/Pages/data.aspx> (accessed October 28, 2016).
- Pandyan, A. D., G. R. Johnson, C. I. Price, R. H. Curless, M. P. Barnes, and H. Rodgers. 1999. A review of the properties and limitations of the Ashworth and modified Ashworth scales as measures of spasticity. *Clinical Rehabilitation* 13(5):373–383.
- Pandyan, A. D., M. Gregoric, M. P. Barnes, D. E. Wood, F. V. Wijck, J. H. Burridge, H. J. Hermens, and G. R. Johnson. 2005. Spasticity: Clinical perceptions, neurological realities and meaningful measurement. *Disability and Rehabilitation* 27(1-2):1–2.
- Pazos, M. R., O. Sagredo, and J. Fernandez-Ruiz. 2008. The endocannabinoid system in Huntington’s disease. *Current Pharmaceutical Design* 14(23):2317–2325.
- PDF (Parkinson’s Disease Foundation). 2016a. What is Parkinson’s disease? http://www.pdf.org/en/about_pd (accessed October 18, 2016).
- PDF. 2016b. Statistics on Parkinson’s. http://www.pdf.org/en/parkinson_statistics (accessed October 18, 2016).
- Pertwee, R. G. 2012. Targeting the endocannabinoid system with cannabinoid receptor agonists: Pharmacological strategies and therapeutic possibilities. *Philosophical Transactions of the Royal Society of London—Series B: Biological Sciences* 367(1607):3353–3363.
- Phillips, R. S., A. J. Friend, F. Gibson, E. Houghton, S. Gopaul, J. V. Craig, and B. Pizer. 2016. Antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood. *Cochrane Database of Systematic Reviews* (2):CD007786.

- Pinto, L., A. A. Izzo, M. G. Cascio, T. Bisogno, K. Hospodar-Scott, D. R. Brown, N. Mascolo, V. Di Marzo, and F. Capasso. 2002. Endocannabinoids as physiological regulators of colonic propulsion in mice. *Gastroenterology* 123:227–234.
- Prud'homme, M., R. Cata, and D. Jutras-Aswad. 2015. Cannabidiol as an intervention for addictive behaviors: A systematic review of the evidence. *Substance Abuse: Research and Treatment* 9:33–38.
- Prum, Jr., B. E., L. F. Rosenberg, S. J. Gedde, S. L. Mansberger, J. D. Stein, S. E. Moroi, L. W. Herndon, Jr., M. C. Lim, and R. D. Williams. 2016. Primary open-angle glaucoma Preferred Practice Pattern® guidelines. *Ophthalmology* 123(1):P41–P111.
- Redler, R. L., and N. V. Dokholyan. 2012. Chapter 7—The Complex Molecular Biology of Amyotrophic Lateral Sclerosis (ALS). In *Progress in Molecular Biology and Translational Science*. Volume 107, edited by B. T. David. Cambridge, MA: Academic Press. Pp. 215–262.
- Richards, B. L., S. L. Whittle, D. M. Van Der Heijde, and R. Buchbinder. 2012. Efficacy and safety of neuromodulators in inflammatory arthritis: A Cochrane systematic review. *Journal of Rheumatology* 39(Suppl 90):28–33.
- Rocha, F. C. M., J. G. dos Santos, Jr., S. C. Stefano, and D. X. da Silveira. 2014. Systematic review of the literature on clinical and experimental trials on the antitumor effects of cannabinoids in gliomas. *Journal of Neuro-Oncology* 116(1):11–24.
- Rosenberg, E. C., R. W. Tsien, B. J. Whalley, and O. Devinsky. 2015. Cannabinoids and epilepsy. *Neurotherapeutics* 12(4):747–768.
- Rossi, S., G. Bernardi, and D. Centonze. 2010. The endocannabinoid system in the inflammatory and neurodegenerative processes of multiple sclerosis and of amyotrophic lateral sclerosis. *Experimental Neurology* 224(1):92–102.
- Russo, E. B., G. W. Guy, and P. J. Robson. 2007. Cannabis, pain, and sleep: Lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. *Chemistry & Biodiversity* 4(8):1729–1743.
- Sandyk, R., and G. Awerbuch. 1988. Marijuana and Tourette's syndrome. *Journal of Clinical Psychopharmacology* 8:444–445.
- Sateia, M. J. 2014. International classification of sleep disorders, third edition: Highlights and modifications. *Chest* 146(5):1387–1394.
- Schauer, G. L., B. A. King, R. E. Bunnell, G. Promoff, and T. A. McAfee. 2016. Toking, vaping, and eating for health or fun: Marijuana use patterns in adults, U.S., 2014. *American Journal of Preventive Medicine* 50(1):1–8.
- Shen, M., and S. A. Thayer. 1998. Cannabinoid receptor agonists protect cultured rat hippocampal neurons from excitotoxicity. *Molecular Pharmacology* 54:459–462.
- Sieradzan, K. A., S. H. Fox, M. Hill, J. P. R. Dick, A. R. Crossman, and J. M. Brotchie. 2001. Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: A pilot study. *Neurology* 57(11):2108–2111.
- Smith, L. A., F. Azariah, T. C. V. Lavender, N. S. Stoner, and S. Bettioli. 2015. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. *Cochrane Database of Systematic Reviews* (11):CD009464.
- Snedecor, S. J., L. Sudharshan, J. C. Cappelleri, A. Sadosky, P. Desai, Y. J. Jalundhwala, and M. Botteman. 2013. Systematic review and comparison of pharmacologic therapies for neuropathic pain associated with spinal cord injury. *Journal of Pain Research* 6:539–547.
- Strasser, F., D. Luftner, K. Possinger, G. Ernst, T. Ruhstaller, W. Meissner, Y. D. Ko, M. Schnelle, M. Reif, and T. Cerny. 2006. Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: A multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the cannabis-in-cachexia-study-group. *Journal of Clinical Oncology* 24(21):3394–3400.

- Timpone, J. G., D. J. Wright, N. Li, M. J. Egorin, M. E. Enama, J. Mayers, and G. Galetto. 1997. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. *AIDS Research and Human Retroviruses* 13(4):305–315.
- Todaro, B. 2012. Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting. *Journal of the National Comprehensive Cancer Network* 10(4):487–492.
- Tomida, I., A. Azuara-Blanco, H. House, M. Flint, R. Pertwee, and P. Robson. 2007. Effect of sublingual application of cannabinoids on intraocular pressure: A pilot study. *Journal of Glaucoma* 15(5):349–353.
- Tzadok, M., S. Uliel-Siboni, I. Linder, U. Kramer, O. Epstein, S. Menascu, A. Nissenkorn, O. B. Yosef, E. Hyman, D. Granot, M. Dor, T. Lerman-Sagie, and B. Ben-Zeev. 2016. CBD-enriched medical cannabis for intractable pediatric epilepsy: The current Israeli experience. *Seizure* 35:41–44.
- Uribe Roca, M., F. Micheli, and R. Viotti. 2005. Cannabis sativa and dystonia secondary to Wilson's disease. *Movement Disorders* 20(1):113–115.
- van den Elsen, G. A. H., A. I. A. Ahmed, M. Lammers, C. Kramers, R. J. Verkes, M. A. van der Marck, and M. G. M. Olde Rikkert. 2014. Efficacy and safety of medical cannabinoids in older subjects: A systematic review. *Ageing Research Reviews* 14(1):56–64.
- van den Elsen, G. A. H., A. I. A. Ahmed, R. J. Verkes, C. Kramers, T. Feuth, P. B. Rosenberg, M. A. van der Marck, and M. G. M. Olde Rikkert. 2015. Tetrahydrocannabinol for neuropsychiatric symptoms in dementia: A randomized controlled trial. *Neurology* 84(23):2338–2346.
- van Laere, K., C. Casteels, I. Dhollander, K. Goffin, L. Grachev, G. Bormans, and W. Vandenberghe. 2010. Widespread decrease of type 1 cannabinoid receptor availability in Huntington disease in vivo. *Journal of Nuclear Medicine* 51(9):1413–1417.
- Volicer, L., M. Stelly, J. Morris, J. McLaughlin, and B. J. Volicer. 1997. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry* 12(9):913–919.
- Wade, D. T., C. Collin, C. Stott, and P. Duncombe. 2010. Meta-analysis of the efficacy and safety of sativex (nabiximols) on spasticity in people with multiple sclerosis. *Multiple Sclerosis* 16(6):707–714.
- Wallace, M. S., T. D. Marcotte, A. Umlauf, B. Gouaux, and J. H. Atkinson. 2015. Efficacy of inhaled cannabis on painful diabetic neuropathy. *Journal of Pain* 16(7):616–627.
- Walther, S., R. Mahlberg, U. Eichmann, and D. Kunz. 2006. Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. *Psychopharmacology* 185(4):524–528.
- Weber, M., B. Goldman, and S. Truniger. 2010. Tetrahydrocannabinol (THC) for cramps in amyotrophic lateral sclerosis: A randomised, double-blind crossover trial. *Journal of Neurology, Neurosurgery & Psychiatry* 81(10):1135–1140.
- Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *Journal of the American Medical Association* 313(24):2456–2473.
- Wilsey, B. L., R. Deutsch, E. Samara, T. D. Marcotte, A. J. Barnes, M. A. Huestis, and D. Le. 2016. A preliminary evaluation of the relationship of cannabinoid blood concentrations with the analgesic response to vaporized cannabis. *Journal of Pain Research* 9:587–598.
- Wong, B. S., M. Camilleri, D. Eckert, P. Carlson, M. Ryks, D. Burton, and A. R. Zinsmeister. 2012. Randomized pharmacodynamic and pharmacogenetic trial of dronabinol effects on colon transit in irritable bowel syndrome–diarrhea. *Neurogastroenterology & Motility* 24(4):358–e169.
- Wright, K., N. Rooney, M. Feeney, J. Tate, D. Robertson, M. Welham, and S. Ward. 2005. Differential expression of cannabinoid receptors in the human colon: Cannabinoids promote epithelial wound healing. *Gastroenterology* 129(2):437–453.

- Zadikoff, C., P. Wadia, J. Miyasaki, R. Char, A. Lang, J. So, and S. Fox. 2011. Cannabinoid, CB1 agonists in cervical dystonia: Failure in a phase IIa randomized controlled trial. *Basal Ganglia* 1(2):91–95.
- Zajicek, J., J. Hobart, A. Slade, and P. Mattison. 2012. Multiple sclerosis and extract of cannabis: Results of the MUSEC trial. *Journal of Neurology, Neurosurgery & Psychiatry* 83(11):1125–1132.

Part III

Other Health Effects

5

Cancer

Chapter Highlights

- The evidence suggests that smoking cannabis does not increase the risk for certain cancers (i.e., lung, head and neck) in adults.
- There is modest evidence that cannabis use is associated with one subtype of testicular cancer.
- There is minimal evidence that parental cannabis use during pregnancy is associated with greater cancer risk in offspring.

Cancer is a major public health problem in the United States. With 1,685,210 new cancer cases and 595,690 cancer-related deaths expected to occur in 2016, it is a leading cause of disease and death among Americans (NCI, 2016). Cannabis use has been associated with cigarette smoking—to which 28.6 percent of all cancer deaths in the United States in 2014 have been attributed—and, like tobacco smoke, cannabis smoke contains carcinogens (Lortet-Tieulent et al., 2016; Tashkin, 2013). These potential risk factors for cancer have prompted epidemiological research examining the association between cannabis use and the risk of developing several types of cancer, including lung, head and neck, testicular, esophageal, and other cancers that occur in adults, as well as cancers that occur in children. The present chapter reviews the findings of three recent, good- to fair-quality systematic reviews, including one pooled analysis, as well as three pri-

mary literature articles that best address the committee's research questions of interest. Study limitations and research gaps are noted, and the strength of the available evidence is weighed in six formal conclusions.

CANCER

Is There an Association Between Cannabis Use and the Incidence of Lung Cancer?

Systematic Reviews

Zhang et al. (2015) pooled data on 2,159 lung cancer cases and 2,985 controls from six case-control studies, four of which were unpublished. The impact of key characteristics of cannabis smoking (e.g., intensity and duration of cannabis smoking, cumulative exposure, age at start of smoking) on lung cancer incidence was evaluated for all study participants and for a subgroup who were not tobacco smokers. Among all study participants there was no statistically significant difference in the risk of lung cancer for habitual cannabis smokers as compared to non-habitual smokers (odds ratio [OR], 0.96, 95% confidence interval [CI] = 0.66–1.38); similarly, among participants who did not smoke tobacco, the risk of lung cancer was not significantly higher or lower for habitual cannabis smokers than for non-habitual cannabis smokers (OR, 1.03, 95% CI = 0.51–2.08).¹ When only adenocarcinoma cases were compared to controls, Zhang et al. (2015, p. 898) observed a “suggestive,” but still statistically nonsignificant, association between lung cancer incidence and either smoking more than 1 joint per day (OR, 1.73, 95% CI = 0.75–4.00) or having a cumulative exposure of more than 10 joint-years (OR, 1.74, 95% CI = 0.85–3.56).

Primary Literature

Huang et al. (2015) conducted an epidemiologic review on the association between cannabis use and the incidence of several cancers, including lung cancer. They evaluated six studies on lung cancer, including Zhang et al. (2015) and two studies included in that review. Of the three remaining studies, two were described by Zhang et al. (2015) as having several limitations, including an inability to adequately control for tobacco use and potential reporting bias, and are not discussed here. The third study

¹ Non-habitual cannabis smokers were defined as those with cumulative cannabis consumption of less than 1 joint-year, including never users. Subjects who did not smoke tobacco were those who reported smoking less than 100 cigarettes over their lifetime, or who fit the cutoffs used in the pooled studies.

evaluated lung cancer risk among 49,321 Swedish male military conscripts over a 40-year period and found that, compared with participants who had reported never using cannabis, those who reported using cannabis more than 50 times at baseline had a statistically significant risk of developing lung cancer (hazard ratio [HR], 2.12, 95% CI = 1.08–4.14) after adjusting for tobacco and alcohol use and other confounders (Callaghan et al., 2013).²

Discussion of Findings

Zhang et al. (2015) found no statistically significant association between smoking cannabis and lung cancer incidence; this was true for all study participants as well as for the subgroup of study participants who were not tobacco smokers. Although the risk of lung cancer increased as the duration and intensity of cannabis use increased, even participants who smoked most often and for the longest periods of time were not at significantly greater risk than non-habitual smokers. Huang et al. (2015) did not perform a meta-analysis of the lung cancer studies; studies included in that review but not in Zhang et al. (2015) indicate an increased risk for lung cancer associated with smoking cannabis.

Both studies noted several limitations. Zhang et al. (2015) were unable to account for potential effect measure modifiers, including those related to variations in cannabis smoking techniques and in the characteristics of the cannabis smoked. The authors also noted that the small number of participants who were heavy and chronic cannabis users rendered effect estimates for these subgroups imprecise. Finally, the study relied on self-report without biological validation to assess patterns of cannabis, making it impossible to verify the accuracy of cannabis use data. Regarding Callaghan et al. (2013), detailed information on cannabis and tobacco use before and after baseline was lacking; the study did not adjust or account for tobacco or cannabis during the 40-year follow-up period; the authors were unaware whether study participants mixed tobacco and cannabis; and the self-reporting process was not anonymized.

CONCLUSION 5-1 There is moderate evidence of no statistical association between cannabis smoking and the incidence of lung cancer.

² There were 49,321 participants at the start of the study, and 44,257 participants involved in the assessment of cannabis risk. Hazard ratio (HR) includes adjustments for tobacco smoking, alcohol consumption, respiratory conditions, and socioeconomic status at time of conscription.

Is There an Association Between Cannabis Use and the Incidence of Head and Neck Cancers?

Systematic Reviews

De Carvalho et al. (2015) conducted a systematic review and meta-analysis of nine case-control studies derived from six articles and totaling 13,931 study participants (5,732 cases and 8,199 controls) in order to evaluate the association between cannabis use and the incidence of head and neck cancers, including upper aerodigestive tract, oral cavity, and nasopharyngeal cancers as well as on head and neck squamous cell carcinoma. After adjusting for tobacco use, age, gender, and race, the meta-analysis found no significant association between cannabis use and head and neck cancers (OR, 1.021, 95% CI = 0.912–1.143). The authors concluded that there was “insufficient epidemiological evidence to support a positive or negative association of marijuana use and the development of [head and neck cancers]” (de Carvalho et al., 2015, p. 1755).

Primary Literature

The committee did not identify any good-quality primary literature that reported on the association between cannabis use and head and neck cancers and were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Discussion of Findings

In their review, de Carvalho et al. (2015) noted several limitations particular to individual studies. First, although a nonsignificant association was observed for head and neck cancers as a group, this finding does not preclude the existence of a significant positive or negative association between cannabis use and the incidence of specific types of head and neck cancer. The systematic review also relied on cohort studies, which may not detect less pronounced risks or risks that emerge over longer periods. Finally, differences in the methods employed in these studies prevented an analysis of how the characteristics of cannabis use (e.g., frequency, duration, method) affect the risk of head and neck cancers.

CONCLUSION 5-2 There is moderate evidence of no statistical association between cannabis use and the incidence of head and neck cancers.

Is There an Association Between Cannabis Use and the Incidence of Testicular Cancer?

Systematic Reviews

Gurney et al. (2015) conducted a systematic review and meta-analysis on the association between cannabis use and testicular germ cell tumors. The authors identified three case-control studies totaling 2,138 study participants (719 cases and 1,419 controls). Compared to participants who never smoked cannabis, participants who reported ever smoking cannabis had a statistically nonsignificant increased risk of developing testicular germ cell tumors (OR, 1.19, 95% CI = 0.72–1.95). By comparison, statistically significant associations between cannabis use and the risk of developing testicular germ cell tumors were seen for the subgroups of participants who were current smokers (OR, 1.62, 95% CI = 1.13–2.31) or who reported smoking cannabis at least once a week (OR, 1.92, 95% CI = 1.35–2.72) or for 10 years or longer (OR, 1.50, 95% CI = 1.08–2.09). Among current users, including the subgroups of those who used cannabis at least once weekly or for at least 10 years, the risk of developing non-seminoma tumors was higher than the risk of developing seminoma tumors. For example, compared to never smokers, participants who smoked at least once per week had a statistically significant risk of developing non-seminoma tumors (OR, 2.59, 95% CI = 1.60–4.19), while the risk for developing seminoma tumors was not statistically significant (OR, 1.27, 95% CI = 0.77–2.11). Gurney et al. (2015) observed that because non-seminoma tumors are frequently diagnosed at a younger age than seminoma tumors the stronger association between cannabis use and non-seminoma tumors suggests “puberty (rather than later in life) as the key point of exposure” (Gurney et al., 2015, p. 8).

Primary Literature

Huang et al. (2015) conducted a review and meta-analysis of the same three studies reviewed by Gurney et al. (2015) and found no association between participants who had ever smoked cannabis and the risk of developing testicular cancer. However, compared to participants who had never smoked cannabis, heavy users who had smoked one or more times per day or week (OR, 1.56, 95% CI = 1.09–2.23) and chronic users who had smoked for 10 years or longer (OR, 1.50, 95% CI = 1.08–2.09) had a statistically significant risk of developing testicular cancer.

Discussion of Findings

Gurney et al. (2015) found a statistically significant association between current, frequent, or chronic cannabis use and the incidence of non-seminoma-type testicular germ cell tumors. By comparison, cannabis use was not associated with a statistically significant risk of developing seminoma-type testicular germ cell tumors. Lacking further evidence, an extrapolation of this association to other types of testicular cancer is unwarranted. Huang et al. (2015) found an association between the incidence of testicular cancer (without further specification) and cannabis use that was frequent or of long duration.

Gurney et al. (2015) highlighted several limitations of their review. First, each of the three case-control studies informing the review relied on self-report without biological validation, and the two studies that utilized interviews to collect this data did not indicate whether the interviewers were blinded to the case-control status of the participants. Self-report data cannot be verified, and unblinded interviewers are a potential source of bias. Second, two of the studies reported response rates that were both low and unequal: 67.5 percent to 38.2 percent response rate for cases and 73.3 percent to 43.3 percent response rate for controls. Differences in the prevalence of cannabis use among participants who did and did not respond could bias the odds ratios calculated in these studies. Third, the high and growing prevalence of cannabis use in the general population may render the category “ever-smoker” uninformative, since it will encompass not only frequent and chronic users but also individuals who have only minimal exposure to the drug. A final limitation is that the studies informing the review did not all control for the same, potentially relevant confounders: three studies controlled for age and a history of cryptorchidism, two controlled for alcohol and drug use, and only one controlled for other substance use.

As noted in Gurney et al. (2015), Huang et al. (2015) did not distinguish between seminoma and non-seminoma-type tumors and also failed to assess the quality of the reviewed studies. Additionally, the review included limited information on the methods used to conduct the meta-analysis.

CONCLUSION 5-3 There is limited evidence of a statistical association between current, frequent, or chronic cannabis smoking and non-seminoma-type testicular germ cell tumors.

Is There an Association Between Cannabis Use and the Incidence of Esophageal Cancers?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and esophageal cancer.

Primary Literature

The committee identified one primary research study that addressed a potential association with esophageal cancer. To assess the association between cannabis use and the incidence of lung and upper aerodigestive tract cancers, Hashibe et al. (2006) conducted a large population-based case-control study involving 1,040 controls and 1,212 cases, 108 of which were diagnosed with esophageal cancer. Investigators collected data on the use of cannabis, tobacco, and alcohol as well as relevant medical, environmental, and socioeconomic information. After adjustments were made for demographic factors and alcohol and tobacco use, study participants with cumulative cannabis exposure equal to 1 to 10 joint-years were found to have a statistically nonsignificant decreased risk of developing esophageal cancer compared to participants who never used cannabis (OR, 0.77, 95% CI = 0.36–1.6). The risk was further depressed, but still not statistically significant, for participants whose cumulative cannabis exposure was equal to 30 or more joint-years (OR, 0.53, 95% CI = 0.22–1.3). Among participants who never smoked cigarettes, the risk of esophageal cancer was not statistically different between those who had ever smoked cannabis and those who had never smoked cannabis (OR, 0.79, 95% CI = 0.30–2.1).

Discussion of Findings

In conducting their investigation, Hashibe et al. (2006) addressed several methodological issues of previous studies of the association between cannabis use and cancer incidence. These issues included accounting for tobacco use and other confounders, avoiding measurement errors, and protecting the anonymity of participants. On account of these efforts to preemptively address methodological issues, few limitations were identified that could account for the lower risk of esophageal cancer among cannabis smokers as compared to nonsmokers—an unexpected, though not statistically significant, result. The participation rate among esophageal cases was low at 35 percent, creating a potential source of bias if the prevalence of cannabis use was much higher or lower among nonpartici-

pants with esophageal cancer than among participants with esophageal cancer. The subgroup of participants with esophageal cancer and high levels of cumulative cannabis exposure (i.e., ≥ 30 joint-years) was relatively small ($n = 9$), thereby limiting the ability to detect an association between cannabis use and cancer incidence in this group. As with other studies, confounders may not have been entirely controlled for, and measurement errors may have persisted. The authors note these potential limitations, but they also speculate that “it is possible that such inverse associations may reflect a protective effect of marijuana” (Hashibe et al., 2006, p. 1833).

CONCLUSION 5-4 There is insufficient evidence to support or refute a statistical association between cannabis smoking and the incidence of esophageal cancer.

Is There an Association Between Cannabis Use and the Incidence of Other Cancers in Adults?

Systematic Reviews

The committee identified no systematic reviews on the association between cannabis exposures and the incidence of other cancers.

Primary Literature

In an epidemiologic review, Huang et al. (2015) reported on the association between cannabis use and the risk of several types of cancer. A cohort study involving 27,920 men and 36,935 women ages 15 to 49 years found that, compared to participants who did not smoke cannabis, self-reported current or former use of cannabis on more than six occasions was associated with prostate cancer in men who never smoked cigarettes (relative risk [RR], 3.1, 95% CI = 1.0–9.5) and with cervical cancer in women who never smoked cigarettes (RR, 1.6, 95% CI = 1.2–2.2), after adjusting for age, race, education, and alcohol use (Sidney et al., 1997). However, when compared to participants who did not smoke cannabis or who had smoked cannabis on only one to six occasions, those who were current or former cannabis smokers were not at statistically significant risk of developing prostate or cervical cancer, after adjusting for tobacco and alcohol use and other potential confounders.

Another large cohort study involving 133,881 participants ages 25 years and older found that, compared to nonuse of cannabis, self-reported cannabis use at least once per month was associated with a statistically significant risk of malignant adult-onset glioma compared to nonuse of cannabis, after controlling for potential confounders, including demo-

graphic and socioeconomic factors and alcohol and tobacco use (RR, 2.8, 95% CI = 1.3–6.2) (Efird et al., 2004). Compared to participants who did not use cannabis, there was statistically significant risk of developing a brain tumor among those participants who reported using cannabis weekly (RR, 3.2, 95% CI = 1.1–9.2) or monthly (RR, 3.6, 95% CI = 1.3–10.2).

Huang et al. (2015) also reviewed two studies on non-Hodgkin lymphoma risk. Holly et al. (1999) conducted a population-based case-control study involving 3,376 women and heterosexual men to determine risk factors for non-Hodgkin lymphoma. Compared to participants who never used cannabis, those who reported using cannabis less than 40 times had a statistically significant decreased risk of developing non-Hodgkin lymphoma, after adjusting for age, sex, and education (OR, 0.68, 95% CI = 0.55–0.84). Among participants who used cannabis on 40 or more occasions, the risk of non-Hodgkin lymphoma was further depressed (OR, 0.57, 95% CI = 0.44–0.74). In another population-based case-control study, 378 HIV-negative men and women diagnosed with non-Hodgkin lymphoma were matched by age, biological sex, race, language of interview, and neighborhood of residence at time of diagnosis to HIV-negative controls (Nelson et al., 1997). There was no statistically significant difference in the risk of developing non-Hodgkin lymphoma among participants who reported using cannabis at any time as compared to those who reported never using cannabis (OR, 0.86, 95% CI = 0.50–1.48). The lack of a statistical difference in non-Hodgkin lymphoma risk between cannabis users and nonusers was true whether participants reported using cannabis only 1 to 5 times (OR, 0.68, 95% CI = 0.34–1.38) or on more than 900 occasions (OR, 1.09, 95% CI = 0.48–2.48).

Other studies reviewed by Huang et al. (2015) examined the association between cannabis use and the risk of Kaposi's sarcoma and penile and anal cancer. Maden et al. (1993) conducted a case-control study involving 110 cases and 355 age-matched controls to identify risk factors for penile cancer. After adjusting for alcohol and cigarette use, age, and number of sexual partners, there was no statistically significant difference in the risk of developing penile cancer among participants who reported ever using cannabis as compared to those who never used cannabis (OR, 1.5, 95% CI = 0.7–3.2). In a case-control study on risk factors for anal cancer, 148 men and women diagnosed with anal cancer were matched by age, biological sex, year of diagnosis, and area of residence to 166 male and female controls diagnosed with colon cancer (Daling et al., 1987). There was no statistically significant difference in the risk of anal cancer among participants who had ever used cannabis as compared to those who had never used cannabis, after adjusting for age, residence, and cigarette use (RR, 0.8, 95% CI = 0.2–4.0). Chao et al. (2009) conducted a cohort study to determine the association between use of cannabis and other recreational

drugs and the risk of Kaposi's sarcoma in homosexual men coinfectd with HIV and human herpes virus 8 (HHV-8). Among 1,335 participants, those who used cannabis in the 6 months preceding data collection were not significantly more likely to develop Kaposi's sarcoma than participants who did not use cannabis during that period (HR, 1.00, 95% CI = 0.79–1.28), after adjusting for potential confounders, including alcohol use, tobacco smoking, and characteristics of sexual activity.

To assess the association between cannabis use and bladder cancer risk, Thomas et al. (2015) reviewed data from 84,170 men ages 45 to 69 years who were participants in the California Men's Health Study. After adjusting for age, race, and body mass index, the risk of developing bladder cancer was significantly reduced for participants who used cannabis but not tobacco, compared to those who used neither cannabis nor tobacco (HR, 0.55, 95% CI = 0.31–1.00). After stratifying cannabis use by levels of cumulative cannabis exposure, the authors found that the depression in bladder cancer risk was statistically significant only for participants who reported smoking cannabis on 3–10 occasions (HR, 0.57, 95% CI = 0.34–0.96). Similarly, stratification by participant age revealed that, among participants who smoked cannabis but not tobacco, the risk of bladder cancer was significantly decreased only for those ages 45 to 54 years (HR, 0.26, 95% CI = 0.07–0.92). In a case-control study involving 52 Veterans Affairs patients younger than 61 years old and age-matched to 104 controls, Chacko et al. (2006) found that a significantly higher proportion of cases as compared to controls reported ever using cannabis (88.5 percent versus 69.2 percent, $p = 0.008$). The mean number of joint-years of cannabis smoked was also significantly higher among cases than controls (48.0 joint-years versus 28.5 joint-years, $p = 0.022$). After adjusting for potential confounders, including tobacco use, a statistically significant association between increasing joint-years of cannabis and the risk of transitional cell carcinoma remained (p trend = 0.01).

Discussion of Findings

Huang et al. (2015, p. 26) reviewed eight studies that reported on the association between cannabis use and prostate, cervical, anal, bladder, and penile cancer, as well as glioma, non-Hodgkin lymphoma, and Kaposi's sarcoma, and they concluded that "there are still insufficient data to make any conclusions on an association with marijuana." Separately, Thomas et al. (2015) found no statistically significant difference in the risk of developing bladder cancer among participants who used cannabis but not tobacco as compared to those who used neither. These studies have several limitations.

In the study on cervical and prostate cancers, Sidney et al. (1997,

p. 727) relied on self-report to determine patterns of cannabis use and did not assess for changes in those patterns during follow-up. The study cohort included no participants older than 49 years of age at baseline, and participants were followed for a mean of 8.6 years; consequently, the study was unable to ascertain whether there is an association between cannabis use and the incidence of cancer in older populations. The authors stated that they “do not consider any of the findings to be conclusive.”

In the study on malignant adult-onset glioma, investigators did not assess for changes in patterns of cannabis use after baseline; only a small number of cases ($n = 8$) reported using cannabis at least once per month, and more than one in four cases (26 percent) did not provide data on cannabis use (Efird et al., 2004). Holly et al. (1999) note that responses to questions concerning events that occurred many years previously (e.g., lifetime cannabis use) or addressing sensitive topics (e.g., illegal drug use) can be affected by recall and response biases, respectively. Nelson et al. (1997) also list recall bias as a potential limitation. Of these two studies, Huang et al. (2015) note that the association between cannabis use and risk of non-Hodgkin lymphoma may be the result of confounding cause by the observed protective association of sexual behavior and cocaine use. For a discussion on the effectiveness of cannabis and cannabinoids as a treatment for glioma and other cancers, see Chapter 4.

Maden et al. (1993) assert that the low rate of participation among cases (50.2 percent) and controls (70.3 percent) was a major limitation of their study on penile cancer. In the study on anal cancer, Daling et al. (1987) note that all control participants were diagnosed with colon cancer. Other investigators have noted that this control group may not be appropriate for assessing the association between cannabis use and anal cancer incidence, as cannabis smoking is a potential risk factor for colorectal cancer (Hashibe et al., 2005). Limitations of the study on Kaposi’s sarcoma include the lack of consistent HHV-8 testing for all participants, the use of noncontinuous categories for describing frequency of cannabis use and the resultant potential for ambiguous reporting, and the use of self-report to collect data on patterns of cannabis use (Chao et al., 2009).

Thomas et al. (2015) note that the observational design of their study creates the potential for participation and response biases. Other limitations of the study include the failure to differentiate the risks for bladder cancer associated with current as opposed to former cannabis use, the lack of an evaluation of other potential risk factors for bladder cancer, and the fact that the study findings apply only to men. Findings from Chacko et al. (2006) are limited by a high proportion of ever tobacco smokers among both cases (94.2 percent) and controls (93.3 percent). According to Huang et al. (2015), the limitations of this study also include its small size, the

use of self-report to collect data on cannabis use, and failing to adjust for tobacco smoking—an acknowledged bladder cancer risk factor.

Further research is needed to better characterize whether and how cannabis use is associated with the risk of developing these cancers. Additionally, since important biological distinctions exist among cancers that occur in a given organ, including histological and molecular subtypes, such research will need to separately investigate and identify the risk factors associated with each.

CONCLUSION 5-5 There is insufficient evidence to support or refute a statistical association between cannabis use and the incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer.

Is There an Association Between Parental Cannabis Use and the Incidence of Cancer in Offspring?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between parental cannabis use and subsequent cancer incidence in offspring.

Primary Literature

Huang et al. (2015) reviewed three studies on the association between parental cannabis use and the risk of leukemia. Robison et al. (1989) conducted a case-control study involving 204 cases diagnosed with acute non-lymphoblastic leukemia (ANLL) by 17 years of age that were matched to controls by age, race, and residential location. Maternal use of cannabis during, and in the year preceding, pregnancy was associated with a statistically significant risk of ANLL (RR, 10, $p = 0.005$). By comparison, the risk of ANLL associated with paternal use of cannabis during the same period was not statistically significant (RR, 1.47, $p = 0.32$). Children whose mothers used cannabis during, or in the year preceding, pregnancy were significantly younger in the age at diagnosis of ANLL than children whose mothers did not use cannabis during this period (37.7 months [mean] versus 96.1 months [mean], $p = 0.007$). There was also a statistically significant difference in the distribution of morphological types of ANLL cases between the cases and the controls ($p = 0.02$). For example, M1/M2 and M4/M5 morphologic types respectively comprised 10 percent and 70 percent of ANLL cases among children whose mothers

used cannabis, while they comprised respectively 58 percent and 31 percent of cases among children whose mothers did not use cannabis. Logistic regression to identify independent risk factors for ANLL found that “maternal marijuana use was the single most predictive factor” identified in the study (Robison et al., 1989, p. 1907).

In contrast to these findings, Trivers et al. (2006) conducted a case-control study involving 517 cases diagnosed with acute myeloid leukemia (AML) by 17 years of age and matched to 610 controls by age, race, and residential location, and they found that children whose mothers used cannabis during, or in the 3 months preceding, pregnancy were at significantly lower risk of developing AML than children whose mothers did not use cannabis during that period, after adjusting for household income and parental age and education (OR, 0.43, 95% CI = 0.23–0.80).³ Among children whose mothers reported using cannabis in the 3 months before pregnancy, those whose mothers used cannabis at least once weekly had a lower risk of developing AML than those whose mothers used cannabis less than once weekly (OR, 0.19, 95% CI = 0.06–0.59 versus OR, 0.57, 95% CI = 0.26–1.29). Although overall paternal use of cannabis was significantly associated with the risk of AML (OR, 1.37, 95% CI = 1.02–1.83), there was no statistically significant association between paternal use of cannabis during, and in the 3 months preceding, pregnancy and the risk of AML (OR, 1.02, 95% CI = 0.67–1.53). The authors concluded that “[p]aternal marijuana use is unlikely as a strong risk factor for childhood AML” (Trivers et al., 2006, p. 117).

Finally, Wen et al. (2000) conducted a case-control study to evaluate the association between exposures related to paternal military service, such as cannabis use, and the incidence of AML or acute lymphoblastic leukemia (ALL) in their children. Among 2,343 cases diagnosed with AML or ALL and matched by age, race, biological sex, and residential location to 2,723 controls, participants whose fathers had ever used cannabis had a statistically significant risk of developing ALL or AML compared to those whose fathers had never used cannabis (OR, 1.5, $p < 0.01$).

Huang et al. (2015) also reviewed studies on the association between parental cannabis use and the incidence of rhabdomyosarcoma, neuroblastoma, and astrocytoma in pediatric populations. A case-control study of 322 children younger than 21 years of age and diagnosed with rhabdomyosarcoma matched by age, race, and biological sex to 322 controls found that children whose mothers used cannabis in the 12 months before their child’s birth were significantly more likely to develop the disease than children whose mothers had not used cannabis during this

³ Acute myeloid leukemia and acute non-lymphoblastic leukemia refer to the same type of cancer.

period (OR, 3.0, 95% CI = 1.4–6.5), after adjusting for complications during pregnancy and other potential confounders (Grufferman et al., 1993). Similarly, children whose fathers used cannabis in the year prior to their child's birth were at significantly greater risk of developing rhabdomyosarcoma than children whose fathers did not use cannabis at this time (OR, 2.0, 95% CI = 1.3–3.3). However, use of cannabis and cocaine were highly correlated, as was maternal and paternal use of cannabis, making it impossible to isolate the effects of maternal and paternal cannabis use from each other or from the effects of parental cocaine use.

Kuijten et al. (1990) conducted a case-control study involving 163 cases diagnosed by 14 years of age with astrocytoma or related tumors and matched to controls by age, race, and residential location, and they found a borderline statistically significant association between maternal use of cannabis in the 10 months preceding their child's birth and the risk of astrocytoma (OR, 2.8, 95% CI = 0.9–9.9, $p = 0.07$).⁴ By comparison, maternal use in the 9 months preceding their child's birth was not associated with the risk of astrocytoma (OR, 4.0, $p = 0.11$).

Bluhm et al. (2006) examined the association between maternal cannabis use and the risk of neuroblastoma in their offspring. Among 538 cases diagnosed with neuroblastoma by 19 years of age—age-matched to 504 controls—maternal use of cannabis during pregnancy, as compared to nonuse of cannabis during any measured time period, was significantly associated with greater risk of neuroblastoma in their offspring, after adjusting for use of other recreational drugs (OR, 2.51, 95% CI = 1.18–5.83). After stratifying maternal use of cannabis by time period, the authors found a statistically significant association between the incidence of neuroblastoma and maternal use of cannabis during the first trimester (OR, 4.75, 95% CI = 1.55–16.48), but not between neuroblastoma incidence and maternal cannabis use in the second or third trimester, in the month preceding conception, or in the period between birth and diagnosis. Age at diagnosis, but not frequency of maternal cannabis use, had large effects on neuroblastoma risk. For example, among children diagnosed with neuroblastoma before 12 months of age, maternal cannabis use was significantly associated with risk of neuroblastoma (OR, 15.61, 95% CI = 3.07–285.89), while the risk was similar for children whose mothers used either less than one or more than one pipeful of cannabis during the first trimester (OR, 4.16, 95% CI = 1.52–14.61 and OR, 4.42, 95% CI = 1.09–29.58).

⁴ Cases were diagnosed with astrocytoma, glioblastoma multiforme, mixed glioma with astrocytic elements, or brainstem glioma.

Discussion of Findings

Findings on the association between parental cannabis use and risk of pediatric leukemia were mixed: maternal cannabis use in the months preceding birth was determined to be at once a risk factor for, and protective against, the development of ANLL/AML in children (Robison et al., 1989; Trivers et al., 2006). Differences in the design of questionnaires employed in these studies, including the extent to which questions on recreational drug use were distinguished from other exposure questions, may have affected participant reporting and contributed to these contradictory results. Limitations of Robison et al. (1989) include findings based on small sample sizes (nine cases), wide confidence intervals for risk estimates, and the possibility that, as a consequence of the large number of parameters analyzed in the study, the association between ANLL incidence and maternal cannabis use was a chance finding. Although the reported frequency of maternal cannabis use was considerably lower in Robison et al. (1989) than in other studies, there was no evidence of difference in reporting between cases and controls. In Trivers et al. (2006), reported rates of maternal cannabis use were lower among cases and higher among controls than in other studies, suggesting the potential for differences in reporting by cases and controls.

While Robison et al. (1989) and Trivers et al. (2006) found that paternal cannabis use during and in the months preceding pregnancy was not associated with ANLL/AML incidence in their offspring, Wen et al. (2000) found that any paternal cannabis use was significantly associated with the incidence of AML or ALL in their offspring. Limitations in Wen et al. (2000) included the potential for selection bias due to a lower participation rate among controls than cases and the potential for residual confounding due to the lack of data on the duration and frequency of exposure to cigarette smoking. A similar lack of data on patterns of cannabis use (e.g., duration, frequency, cumulative exposure) prevented investigation of a dose–response relationship between paternal cannabis use and risk of ALL in their offspring.

Grufferman et al. (1993) found that parental cannabis use was significantly associated with the incidence of rhabdomyosarcoma in their offspring, and Bluhm et al. (2006) found that maternal cannabis use during the first trimester was significantly associated with neuroblastoma. In the latter study, very few mothers reported using cannabis more than once per day during any of the measured time periods, suggesting the potential for underreporting the frequency of cannabis use. Additionally, there was insufficient data to assess dose–response relationships; findings on paternal cannabis use were limited due to low response rates; and confidence intervals were wide due to the small number of women reporting cannabis use during and just before pregnancy. In Grufferman et al.

(1993), 25 percent of cannabis users were also cocaine users. As a result of this correlation, any association between parental cannabis use and risk of rhabdomyosarcoma is confounded by polysubstance use. In addition, the authors did not collect data on frequency and duration of cannabis use and therefore were unable to assess for a dose–response relationship.

CONCLUSION 5-6 There is insufficient evidence to support or refute a statistical association between parental cannabis use and a subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring.

RESEARCH GAPS

To address the research gaps relevant to cancer incidence, the committee suggests the following:

- There is need for robust epidemiological studies to investigate the association between cannabis exposure and several types of cancers, including but not limited to lung, head and neck, testicular, and esophageal cancers.
- Further investigation is needed to resolve any contradictory findings on, and to characterize the nature and strength of, any potential associations between parental cannabis use and the risk of cancer in their offspring.
- To promote the development of a body of high-quality evidence on the association between cannabis exposure and cancer incidence, researchers need to prioritize rigorous study designs and implement data collection protocols and methods that allow them to control for key confounders and to precisely measure cannabis exposure.
- Because of changing exposures to cannabis and the fact that many associations are based on single studies, replication of existing studies in targeted areas is needed.

SUMMARY

The committee identified good- or fair-quality systematic reviews on the association between cannabis use and the risk of lung, testicular, and head and neck cancers. Good-quality primary literature on the association between cannabis use and lung, testicular, esophageal, childhood, and several other cancers was also identified. Due to a paucity of research,

mixed findings, and numerous methodological limitations, the committee judged the evidence from the studies on childhood cancers, esophageal cancer, and various other cancers in adults to be insufficient to support or refute a statistically significant association between cannabis use and the incidence of these cancers. More conclusive findings and less extensive methodological limitations in the literature on lung, testicular, and head and neck cancers allowed the committee to conclude that there is moderate evidence that there is no statistically significant association between cannabis use and the incidence of lung or head and neck cancer, and limited evidence that there is a statistically significant association between current, frequent, or chronic cannabis use and the incidence of non-seminoma-type testicular germ cell tumors. Below, Box 5-1 summarizes the chapter conclusions.

BOX 5-1 Summary of Chapter Conclusions*

There is moderate evidence of *no* statistical association between cannabis use and:

- Incidence of lung cancer (cannabis smoking) (5-1)
- Incidence of head and neck cancers (5-2)

There is limited evidence of a statistical association between cannabis smoking and:

- Non-seminoma-type testicular germ cell tumors (current, frequent, or chronic cannabis smoking) (5-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- Incidence of esophageal cancer (cannabis smoking) (5-4)
- Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer (5-5)
- Subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (parental cannabis use) (5-6)

* Numbers in parentheses correspond to chapter conclusion numbers.

Epidemiological studies that investigate the association between cannabis use and the risk of various cancers face methodological challenges similar to those found in studies of other clinical outcomes. These challenges include, but are not limited to, small sample sizes and low participation rates, the inability to verify cannabis use data based on self-report alone, and difficulties in controlling for potential confounders and accounting for potential effect modifiers. Additionally, some special—if not unique—methodological challenges pertain to cancer studies. For example, cancer is a diverse set of diseases that occur in different organs and organ systems and have different histopathological characteristics and risk factors. Some of these risk factors, such as family cancer history, occupational exposures, and diet, are difficult to measure and were often not accounted for by the studies reviewed in this chapter. Additionally, the long incubation period of many cancers requires a similarly extended observation period, and that makes it difficult to fully characterize the relevant cannabis exposure and to control for other relevant exposures.

Future research will need to address the limited scope and quality of epidemiological studies on the association between cannabis use and cancer incidence. Investigators will need to confirm existing evidence on lung and head and neck cancers and to expand the evidence base on testicular, esophageal, and childhood cancers, as well as other cancers in adults. To address the methodological limitations described above, future studies will also need to be well designed and to employ rigorous methods of data collection and measurement.

REFERENCES

- Bluhm, E. C., J. Daniels, B. H. Pollock, and A. F. Olshan. 2006. Maternal use of recreational drugs and neuroblastoma in offspring: A report from the Children's Oncology Group (United States). *Cancer Causes & Control* 17(5):663–669.
- Callaghan, R. C., P. Allebeck, and A. Sidorchuk. 2013. Marijuana use and risk of lung cancer: A 40-year cohort study. *Cancer Causes & Control* 24(10):1811–1820.
- Chacko, J. A., J. G. Heiner, W. Siu, M. Macy, and M. K. Terris. 2006. Association between marijuana use and transitional cell carcinoma. *Urology* 67(1):100–104.
- Chao, C., L. P. Jacobson, F. J. Jenkins, D. Tashkin, O. Martinez-Maza, M. D. Roth, L. Ng, J. B. Margolick, J. S. Chmiel, Z. F. Zhang, and R. Detels. 2009. Recreational drug use and risk of Kaposi's sarcoma in HIV- and HHV-8-coinfected homosexual men. *AIDS Research and Human Retroviruses* 25(2):149–156.
- Daling, J. R., N. S. Weiss, T. G. Hislop, C. Maden, R. J. Coates, K. J. Sherman, R. L. Ashley, M. Beagrie, J. A. Ryan, and L. Corey. 1987. Sexual practices, sexually transmitted diseases, and the incidence of anal cancer. *New England Journal of Medicine* 317(16):973–977.
- de Carvalho, M. F., M. R. Dourado, I. B. Fernandes, C. T. Araujo, A. T. Mesquita, and M. L. Ramos-Jorge. 2015. Head and neck cancer among marijuana users: A meta-analysis of matched case-control studies. *Archives of Oral Biology* 60(12):1750–1755.

- Efird, J. T., G. D. Friedman, S. Sidney, A. Klatsky, L. A. Habel, N. V. Udaltsova, S. Van den Eeden, and L. M. Nelson. 2004. The risk for malignant primary adult-onset glioma in a large, multiethnic, managed-care cohort: Cigarette smoking and other lifestyle behaviors. *Journal of Neuro-Oncology* 68(1):57–69.
- Grufferman, S., A. G. Schwartz, F. B. Ruymann, and H. M. Maurer. 1993. Parents' use of cocaine and marijuana and increased risk of rhabdomyosarcoma in their children. *Cancer Causes & Control* 4(3):217–224.
- Gurney, J., C. Shaw, J. Stanley, V. Signal, and D. Sarfati. 2015. Cannabis exposure and risk of testicular cancer: A systematic review and meta-analysis. *BMC Cancer* 15:897.
- Hashibe, M., K. Straif, D. P. Tashkin, H. Morgenstern, S. Greenland, and Z. F. Zhang. 2005. Epidemiologic review of marijuana use and cancer risk. *Alcohol* 35(3):265–275.
- Hashibe, M., H. Morgenstern, Y. Cui, D. P. Tashkin, Z. F. Zhang, W. Cozen, T. M. Mack, and S. Greenland. 2006. Marijuana use and the risk of lung and upper aerodigestive tract cancers: Results of a population-based case-control study. *Cancer Epidemiology, Biomarkers & Prevention* 15(10):1829–1834.
- Holly, E. A., C. Lele, P. M. Bracci, and M. S. McGrath. 1999. Case-control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay Area, California. *American Journal of Epidemiology* 150(4):375–389.
- Huang, Y. H., Z. F. Zhang, D. P. Tashkin, B. Feng, K. Straif, and M. Hashibe. 2015. An epidemiologic review of marijuana and cancer: An update. *Cancer Epidemiology, Biomarkers & Prevention* 24(1):15–31.
- Kuijten, R. R., G. R. Bunin, C. C. Nass, and A. T. Meadows. 1990. Gestational and familial risk factors for childhood astrocytoma: Results of a case-control study. *Cancer Research* 50(9):2608–2612.
- Lortet-Tieulent, J., A. Goding Sauer, R. L. Siegel, K. D. Miller, F. Islami, S. A. Fedewa, E. J. Jacobs, and A. Jemal. 2016. State-level cancer mortality attributable to cigarette smoking in the United States. *JAMA Internal Medicine* 176(12):1792–1798.
- Maden, C., K. J. Sherman, A. M. Beckmann, T. G. Hislop, C. Z. Teh, R. L. Ashley, and J. R. Daling. 1993. History of circumcision, medical conditions, and sexual activity and risk of penile cancer. *Journal of the National Cancer Institute* 85(1):19–24.
- NCI (National Cancer Institute). 2016. *SEER stat fact sheet: Cancer of any site*. <https://seer.cancer.gov/statfacts/html/all.html> (accessed December 9, 2016).
- Nelson, R. A., A. M. Levine, G. Marks, and L. Bernstein. 1997. Alcohol, tobacco and recreational drug use and the risk of non-Hodgkin's lymphoma. *British Journal of Cancer* 76(11):1532–1537.
- Robison, L. L., J. D. Buckley, A. E. Daigle, R. Wells, D. Benjamin, D. C. Arthur, and G. D. Hammond. 1989. Maternal drug use and risk of childhood nonlymphoblastic leukemia among offspring. An epidemiologic investigation implicating marijuana (a report from the Childrens Cancer Study Group). *Cancer* 63(10):1904–1911.
- Sidney, S., C. P. Quesenberry, Jr., G. D. Friedman, and I. S. Tekawa. 1997. Marijuana use and cancer incidence (California, United States). *Cancer Causes & Control* 8(5):722–728.
- Tashkin, D. P. 2013. Effects of marijuana smoking on the lung. *Annals of the American Thoracic Society* 10(3):239–247.
- Thomas, A. A., L. P. Wallner, V. P. Quinn, J. Slezak, S. K. Van Den Eeden, G. W. Chien, and S. J. Jacobsen. 2015. Association between cannabis use and the risk of bladder cancer: Results from the California Men's Health Study. *Urology* 85(2):388–392.
- Trivers, K. F., A. C. Mertens, J. A. Ross, M. Steinbuch, A. F. Olshan, and L. L. Robison. 2006. Parental marijuana use and risk of childhood acute myeloid leukaemia: A report from the Children's Cancer Group (United States and Canada). *Paediatric and Perinatal Epidemiology* 20(2):110–118.

- Wen, W. Q., X. O. Shu, M. Steinbuch, R. K. Severson, G. H. Reaman, J. D. Buckley, and L. L. Robison. 2000. Paternal military service and risk for childhood leukemia in offspring. *American Journal of Epidemiology* 151(3):231–240.
- Zhang, L. R., H. Morgenstern, S. Greenland, S. C. Chang, P. Lazarus, M. D. Teare, P. J. Woll, I. Orlov, B. Cox, Y. Brhane, G. Liu, and R. J. Hung. 2015. Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium. *International Journal of Cancer* 136(4):894–903.

6

Cardiometabolic Risk

Chapter Highlight

- The evidence is unclear as to whether and how cannabis use is associated with heart attack, stroke, and diabetes.

An estimated 85.6 million American adults have at least one cardiovascular disease such as heart disease, stroke, heart failure, or hypertension (Mozaffarian et al., 2016). Each year cardiovascular diseases account for more than 800,000 deaths (i.e., they are the underlying cause listed on the death certificate), or 30 percent of all deaths in the United States (Mozaffarian et al., 2016).

Heart disease is the leading cause of mortality in the United States, accounting for more than 600,000 deaths per year (Kochanek et al., 2016). Within subcategories of heart disease, coronary heart disease (CHD) is by far the largest, with 364,000 deaths annually (Kochanek et al., 2016). CHD is a disease in which a waxy substance called plaque builds up inside the blood vessels supplying the heart (i.e., the coronary arteries). Over the course of years or decades, the plaque can harden or rupture, resulting in an inadequate supply of blood to the heart which may, in some instances, result in death of heart muscle (myocardial infarction).

Both coronary heart disease and stroke are associated with aging, with nearly 93 percent of CHD deaths and 94 percent of stroke deaths occurring in individuals 55 years and older (Kochanek et al., 2016). More

than one-third (about 36 percent) of CHD deaths occur in individuals ages 85 years and older, while 43 percent of stroke deaths occur in this age group (Kochanek et al., 2016).

Current (past-month) cannabis use is fairly low in the older populations most likely to experience cardiovascular diseases—in particular, about 2 percent past-month prevalence in those ages 50 years and older. In younger adults, by contrast, the prevalence of cannabis use has been estimated to be as high as 19.6 percent for past-month use among those ages 18 to 25 years (Azofeifa et al., 2016), but these rates decline dramatically with aging. In contrast, tobacco smoking—a known risk factor for heart disease and stroke—has a much higher prevalence among older adults: 18 percent in those ages 45 to 64 years and 8.5 percent in those ages 65 years and older who smoke (Jamal et al., 2015).

Cardiometabolic disorders result in a substantial economic burden on the United States. From 2011 to 2012 the estimated annual cost of cardiovascular diseases, including heart disease, stroke, hypertensive disease, and other circulatory conditions, was \$316.6 billion (\$207.3 billion for heart disease, \$33.0 billion for stroke). The total estimated cost of diagnosed diabetes in 2012 was \$245 billion (Mozaffarian et al., 2016).

The objective of the review of cannabis and cardiometabolic conditions was to assess the independent association of cannabis with these conditions in studies in which the association has been quantified. The justification for examining cannabis use in relation to cardiometabolic conditions is that these conditions are among the leading causes of death; are highly prevalent in the United States; account for high levels of medical care utilization and cost; and are caused, in significant part, by modifiable lifestyle risk factors, including diet, physical activity, and cigarette smoking. The high prevalence of these conditions means that a behavior that is associated with a small degree of increased risk for heart disease, stroke, or diabetes can be associated with a high level of attributable risk, that is, the number of cases of disease that result from that behavior. While the prevalence of cardiometabolic conditions is concentrated in the older-adult age groups which have low rates of cannabis use, it is expected that the expanding legalization of cannabis use will cause the rates of use to increase.

The discussion in this review is limited to acute myocardial infarction, stroke, metabolic dysregulation and metabolic syndrome, and diabetes. Sudden death and arrhythmias such as atrial fibrillation were other topics of interest for which no data were available to quantify the association with cannabis use. The 1999 Institute of Medicine (IOM) report *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999) reviewed the cardiovascular system; however, no conclusions or recommendations related to cannabis use and cardiometabolic outcomes were included in that report.

The literature search conducted by the current committee did not identify any systematic reviews that were rated as “good” or “fair” for cannabis use and acute myocardial infarction, stroke, dyslipidemia or metabolic syndrome, or diabetes, so all of the available primary literature for these outcomes dating back to 1999 was reviewed and the 12 primary articles rated as “good” or “fair” by the committee have been included in this chapter.

ACUTE MYOCARDIAL INFARCTION

Each year, an estimated approximately 550,000 Americans have an incident (i.e., first-time) heart attack (acute myocardial infarction, or AMI) and about 200,000 have a recurrent attack (Mozaffarian et al., 2016). Of those who have a heart attack each year, about 116,000 die as a result of their coronary event (Mozaffarian et al., 2016). The committee responsible for the IOM report *Marijuana and Medicine: Assessing the Science Base* (1999) did not make any conclusions or recommendations regarding cannabis use and acute myocardial infarctions.

The acute cardiovascular effects of cannabis include increases in heart rate and supine blood pressure and postural hypotension (Beaconsfield et al., 1972; Benowitz and Jones, 1981). Smoking cannabis decreases exercise test duration on maximal exercise tests and increases the heart rate at submaximal levels of exercise (Renaud and Cormier, 1986). These acute effects provide a physiological basis for cardiac ischemia to develop in cannabis users. In fact, the time from exercise to the onset of angina pectoris is decreased by smoking one cannabis cigarette (Aronow and Cassidy, 1974). Tolerance develops to the acute effects of tetrahydrocannabinol (THC) over several days to a few weeks (Gorelick et al., 2013). Reported cardiovascular effects that may increase the risk of AMI include irregular heart rate (Khiabani et al., 2008) and impaired vascular endothelial function (demonstrated in rates from exposure to secondhand cannabis smoke) (Wang et al., 2016). Additionally, carbon dioxide production from smoked cannabis decreases the oxygen-carrying capacity of the blood and may contribute to the development of cardiac ischemia.

There have been numerous case reports suggesting that cannabis use is associated with the occurrence of AMI. The two primary studies that have quantified the risk of AMI associated with cannabis use and that were rated as good or fair are reviewed below.

Is There an Association Between Cannabis Use and Acute Myocardial Infarction?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis and AMI. Three descriptive review articles provided useful background: Sidney (2002), Thomas et al. (2014), and Franz and Frishman (2016).

Primary Studies

A retrospective cohort study (Sidney, 2002; Sidney et al., 1997) assessed the risk of hospitalization for AMI associated with cannabis use in a cohort of 62,012 men and women ages 15 through 49 years who had, from mid-1979 through 1985, completed self-administered research questions on their cannabis, tobacco, and alcohol use. AMI was assessed by linkage to electronically maintained records of all overnight hospitalizations in Kaiser Permanente Northern California. Follow-up was conducted for up to 12 years. Current use of cannabis was reported by 22 percent and former use by 20 percent of the cohort. There were 209 incident AMIs, 173 in men and 36 in women. The relative risk associated with cannabis use was assessed by a Cox proportional hazards model with adjustments for age, race, education, body mass index (BMI), history of hypertension, smoking, and alcohol use. The relative risk for AMI in current users was 1.1 (95% confidence interval [CI] = 0.7–1.7) for men and 1.8 (95% CI = 0.5–6.3) for women; in former users it was 0.9 (95% CI = 0.6–1.5) for men and 1.0 (95% CI = 0.2–4.5) for women. Both current and former cannabis use were unassociated with an increased risk of AMI.

Study limitations included a reliance of self-report of cannabis use which may result in misclassification of this exposure; the lack of availability of longitudinal data on cannabis use; and the relatively young age (mean age 33 years), which meant that the AMIs occurred in a relatively young age range that is not representative of the older age range in which the vast majority of AMIs occur. Cannabis use was assessed at only one point in time.

A case crossover study design was used to examine the role of cannabis use as a possible trigger for myocardial infarction in 3,882 AMI patients in an inception cohort study identified between August 1989 and September 1996 from 64 community and tertiary medical centers in the United States that were part of the Determinants of Myocardial Onset Study (Mittleman et al., 2001). The mean ages of cannabis users and abstainers were 43.7 and 62.0 years, respectively, while 68 percent of cannabis users and 32 percent of abstainers were current tobacco smok-

ers. Nine patients (0.2 percent) interviewed soon after admission for AMI reported cannabis use during the hour preceding the symptoms of AMI. The risk for AMI associated with cannabis use during the hour preceding symptoms of AMI was 4.8 (95% CI = 2.9–9.5) as assessed by a case-crossover analysis. The exclusion of three of the nine patients who reported other triggering behaviors during the hour prior to the AMI (cocaine use and/or sexual intercourse) resulted in a relative risk of 3.2 (95% CI = 1.4–7.3).

The major limitations of this study were its small size and its reliance on self-report for cannabis use status, which meant that any misclassification could have had a significant effect on the results. While the case-crossover design controls for confounding by traditional risk factors for cardiovascular disease, it does not control for interaction of these factors, and one cannot determine whether cannabis acts as a trigger in low-risk individuals or those who are nonsmokers of tobacco.

Discussion of Findings

While there are a number of reports of an association between cannabis use and AMI, only the two studies described above quantify risk, with the Sidney (2002) study demonstrating no association with an increased or decreased risk of AMI and the Mittleman et al. (2001) study finding that cannabis use may act as a trigger for AMI. The limitations of these studies were described. More generally, with the Mittleman study as an exception, most reports of adverse cardiovascular effects of cannabis, including AMI, have been conducted in a relatively young age range, while major cardiovascular events are concentrated in older adults and the findings may not be generalizable to this age group. Other general limitations beyond those already mentioned in the description of the studies include the absence of the impact of the route of consumption (e.g, smoked, edible, etc.); dose, including accounting for the content of THC and other cannabinoids and potential additives or contaminants; and total lifetime duration/dose of cannabis use. Overall, the articles were judged to be of fair quality for assessing the risk of acute myocardial infarction associated with cannabis use.

The role of cannabis as a trigger of AMI is plausible, given its cardiostimulatory effects, which may cause ischemia in susceptible hearts. Carboxyhemoglobinemia from combustion of cannabis resulting in a decreased oxygen-carrying capacity of blood may also contribute to ischemia. Given the physiologic plausibility for a trigger effect, smoking cannabis may put individuals, particularly those at high risk for cardiovascular disease, at increased risk for AMI.

CONCLUSION 6-1

- 6-1(a) There is limited evidence of a statistical association between cannabis smoking and the triggering of acute myocardial infarction.**
- 6-1(b) There is no evidence to support or refute a statistical association between chronic effects of cannabis use and the risk of acute myocardial infarction.**

STROKE

Stroke is the fifth leading cause of death in the United States, accounting for 133,000 deaths annually (Kochanek et al., 2016). A stroke is the death of a portion of brain tissue due to a disruption of the blood supply. Strokes may be ischemic (inadequate blood/oxygen supply) or hemorrhagic (bleeding into the brain) in origin. Each year, approximately 795,000 people experience a new or recurrent stroke. Approximately 610,000 of these are first stroke occurrences and 185,000 are recurrent stroke events (Mozaffarian et al., 2016). The committee responsible for the IOM report *Marijuana and Medicine: Assessing the Science Base* (1999) did not make any conclusions or recommendations regarding cannabis use and stroke.

Numerous reports have suggested that smoking cannabis increases the risk of stroke, including case series (Phillips et al., 2011) and studies describing cannabis-associated vascular changes that may be associated with stroke (Herning et al., 2001; Wolff et al., 2011, 2015). Several reports have indicated a close temporal relationship between cannabis smoking and stroke (Wolff et al., 2013). The cardiovascular effects of cannabis that have been proposed as a possible mechanism in the etiology of stroke include orthostatic hypotension with secondary impairment of the auto-regulation of cerebral blood flow, altered cerebral vasomotor function, supine hypertension and swings in blood pressure, cardioembolism with atrial fibrillation, other arrhythmias, vasculopathy, vasospasm, reversible cerebral vasoconstriction syndrome, and multifocal intracranial stenosis (Wolff et al., 2015).

Is There an Association Between Cannabis Use and Stroke?*Systematic Reviews*

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and stroke.

Primary Studies

A large reported study on the association of cannabis and stroke by Rumalla et al. (2016a) used the Nationwide Inpatient Sample, which provides admission data from a 20 percent sample of all U.S. hospitalizations, to examine the cross-sectional association between cannabis use and hospitalization for acute ischemic stroke (AIS) among patients ages 15 to 54 years during the time period 2004–2011. The primary *International Classification of Diseases (ICD)-9-CM* discharge code was used to identify AIS, and current cannabis use was identified using the ICD-9-CM code 340.30, which includes both cannabis dependence and non-dependent cannabis abuse. Current cannabis use was identified in 11,320 of 478,649 AIS events (2.4 percent). Tobacco use prevalence was higher in current cannabis users than in nonusers (64.4 percent versus 31.5 percent) as was cocaine use (26.7 percent versus 3.1 percent). The odds ratio (OR) associated with current cannabis use and hospitalization for AIS was 1.17 (95% CI = 1.15–1.20) as calculated with multivariable logistic regression adjusted for age, gender, race, substance use, payer status, Charlson’s comorbidity index, and other comorbid risk factors. Analyses stratified on tobacco use status were not available. The limitations of this study include the cross-sectional design; the probable under-ascertainment of current cannabis use (2.4 percent is low for this age range); the absence of data on duration of tobacco use; and the absence of analyses that are stratified by tobacco and by cocaine use to determine the OR in non-tobacco use and non-cocaine users, given the high prevalence of these known risk factors for ischemic stroke.

In a case-control study conducted in a New Zealand hospital (Barber et al., 2013), 160 of 218 (73 percent) of ischemic stroke/transient ischemic attack (TIA) patients, ages 18 to 55 years, had urine drug screens between January 2009 and April 2012 (150 ischemic stroke, 10 TIA). Control urine samples were obtained from 160 patients matched for age, sex, and ethnicity. Twenty-five (15.6 percent) of the stroke/TIA patients and 13 (8.1 percent) of the control patients had positive cannabis drug screens. Eighty-eight percent of cannabis-positive patients were current tobacco smokers versus 28 percent of cannabis-negative patients. The OR associated with current cannabis use was 2.30 (95% CI = 1.08–5.08), but it was no longer statistically significant when an additional adjustment was made for tobacco use (1.59, 95% CI = 0.71–3.70).

In a cross-sectional analysis by Westover et al. (2007) of all ischemic (N = 998) and hemorrhagic strokes (N = 937) identified in 2003 by ICD-9 codes from an administrative database maintained by the state of Texas in young adults ages 18 to 44 years the ORs of cannabis and other illicit drugs being associated with ischemic and hemorrhagic stroke were estimated using a multivariable logistic regression adjusting for alcohol,

tobacco, amphetamines, cocaine, opioids, cardiovascular risk factors, and other medical conditions associated with increased risk of these outcomes. The prevalence of cannabis use, identified by ICD-9 codes, was approximately 1 percent. Cannabis was associated with an increased risk of ischemic stroke (OR, 1.76; 95% CI = 1.15–2.71) but was not associated with a risk of hemorrhagic stroke (OR, 1.36; 95% CI = 0.90–2.06). The prevalence rate of tobacco use was not reported, and analyses stratified by category of tobacco use were not performed.

A retrospective cohort study (Sidney, 2002; Sidney et al., 1997) assessed the risk of hospitalization for stroke associated with cannabis use in a cohort of 62,012 men and women of ages 15 to 49 years who had, from mid-1979 through 1985, completed self-administered research questions on cannabis, tobacco, and alcohol use. Stroke was assessed by linkage to electronically maintained records of all overnight hospitalizations in Kaiser Permanente Northern California. Follow-up was conducted for up to 12 years. Current use of cannabis was reported by 22 percent and former use by 20 percent of the cohort. There were 130 incident strokes, 68 in men and 62 in women. The relative risk associated with cannabis use was assessed by Cox proportional hazards model with adjustments for age, race, education, BMI, history of hypertension, smoking, and alcohol use. The relative risk for stroke in current users was 1.0 (95% CI = 0.5–1.9) for men and 0.7 (95% CI = 0.3–2.2) for women; in former users it was 0.8 (95% CI = 0.4–1.8) for men and 1.5 (95% CI = 0.7–3.5) for women. Both current cannabis use and former cannabis use were not associated with increased risk of stroke.

The study's limitations included its reliance on self-report of cannabis use, which may result in misclassification of this exposure; the lack of availability of longitudinal data on cannabis use; and the relatively young age of subjects (mean age 33 years) so that the strokes occurred in a relatively young age range that is not representative of the older age range in which the vast majority of strokes occur. Cannabis use was assessed at only one point in time.

Rumalla et al. (2016b) used the Nationwide Inpatient Sample, which provides admission data from a 20 percent sample of all U.S. hospitalizations, to examine the cross-sectional association between cannabis use and hospitalization for aneurysmal subarachnoid hemorrhage (SAH) among patients ages 15 to 54 years during the time period 2004–2011. The primary ICD-9-CM discharge code was used to identify SAH, and current cannabis use was identified using the ICD-9-CM code 340.30, which includes both cannabis dependence and nondependent cannabis abuse. Current cannabis use was identified in 2,104 of the 94,052 (2.2 percent) SAH events. Tobacco use prevalence was higher in current cannabis users than in nonusers (59.3 percent versus 25.4 percent). The OR associated

with current cannabis use was 1.18 (95% CI = 1.12–1.24) according to a multivariate logistic regression adjusted for age, gender, race, substance use, primary payer status, Charlson's comorbidity index, and other SAH risk factors. The limitations of this study include its cross-sectional design, the probable under-ascertainment of current cannabis use (2.2 percent is low for this age range), the absence of data on duration of cannabis use, and the absence of analyses that are performed stratified by tobacco to determine the OR in non-tobacco use, given the high prevalence of this known risk factor for ischemic stroke.

Discussion of Findings

The studies by Rumalla et al. (2016a,b) and Westover et al. (2007) were cross-sectional studies using administrative data consisting of ICD-9 codes. Cross-sectional studies do not allow one to assess temporality between exposure and outcome. The miscoding of strokes does occur, although the reliability is probably reasonable for epidemiological studies. The classification of exposure status using ICD-9 is particularly concerning, given the likelihood that the percentage of cannabis users appears to be low compared to population norms in each of these studies, most notably the Westover et al. (2007) study.

With the exception of the Sidney (2002) study, none of the studies have data on the temporal relation between the cannabis or tobacco use and the stroke. A general problem was the analytic treatment of tobacco use. Given the much longer duration and frequency of tobacco smoking than of cannabis smoking for most people and the very common co-use of both substances, it is not appropriate to assume that an adjustment for tobacco use in a multivariable model will provide an accurate assessment of the risk associated with cannabis use. Additional analytic approaches, when feasible, may include testing the interaction between cannabis and tobacco use and performing stratified analyses to test the association of cannabis use with clinical endpoints in nonusers of tobacco. Other general limitations beyond those already mentioned in the description of the studies include the absence of the impact of the route of consumption (e.g., smoked, edible, etc.); the absence of information on dose, including accounting for the content of THC and other cannabinoids and potential additives or contaminants; and the lack of information on the total lifetime duration/dose of cannabis use.

All the articles were judged to be of fair quality for assessing the risk of stroke associated with cannabis use. With the exception of Sidney (2002) and Barber et al. (2013), all showed an increased risk of stroke associated with cannabis use but had significant limitations. For ischemic stroke, two of the studies indicated an increased risk while one showed a

nonsignificant finding in the direction of increased risk. For subarachnoid hemorrhage, the single study found an increased risk. For the combined hemorrhagic stroke endpoint assessed by Westover et al. (2007), the study showed no association of cannabis use with the risk of this endpoint.

CONCLUSION 6-2 There is limited evidence of a statistical association between cannabis use and ischemic stroke or subarachnoid hemorrhage.

METABOLIC DYSREGULATION, METABOLIC SYNDROME, PREDIABETES, AND DIABETES MELLITUS

Ranked as the seventh-leading cause of death in the United States, diabetes accounts for more than 76,000 deaths annually (Kochanek et al., 2016). An estimated 29 million adults in the United States have diabetes (CDC, 2014a), which is a group of conditions characterized by high blood glucose (sugar) levels due to the inability to metabolize glucose effectively. The number of new (incident) cases of diabetes diagnosed annually is more than 1.4 million (CDC, 2015). Similar to the case with cardiovascular diseases, the prevalence of diabetes increases with age, from 4.4 percent among those ages 20 to 44 years, to 16.2 percent at ages 45 to 64 years, and 25.9 percent at ages 65 years and older (CDC, 2014a). A major risk factor for the development of the most common type of diabetes (type 2) is obesity, which results in resistance to the effect of the glucose regulating hormone, insulin. An epidemic of obesity has resulted in the prevalence of obesity increasing from 22.9 percent in 1988–1994 to 34.9 percent in 2011–2012 (Flegal et al., 2002; Ogden et al., 2014), contributing to a near tripling of the prevalence of diabetes since 1990 to its current level of 9.3 percent (CDC, 2014b). The committee responsible for the IOM report *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999) did not make any conclusions or recommendations regarding cannabis use and metabolic dysregulation, metabolic syndrome, prediabetes, or diabetes mellitus.

Obesity, most notably central adiposity, is the dominant risk factor for the development of type 2 diabetes (Klil-Drori et al., 2016). Stimulation of the endogenous cannabinoid receptor system (the CB₁ receptor and, to a lesser extent, the CB₂ receptor) by Δ⁹-THC, the major psychoactive component of cannabis, and by endogenous cannabinoids increases appetite and promotes adipogenesis, the production of body fat (Di Marzo et al., 2011). This physiological pathway suggests that cannabinoids such as Δ⁹-THC may promote weight gain, which would increase the risk of an individual developing diabetes.

As noted earlier, the approximately 30-year epidemic of increasing

obesity rates in the United States has been associated with increasing rates of diabetes. A number of studies have examined the association of cannabis use with BMI and obesity. Counterintuitively, the majority of the reviewed studies showed that cannabis was associated with a lower BMI or a lower prevalence of obesity, or both (Hayatbakhsh et al., 2010; Le Strat and Le Foll, 2011; Smit and Crespo, 2001; Warren et al., 2005), or to have no association with BMI or obesity (Rodondi et al., 2006).

Because of the significance of diabetes as a highly prevalent disease, as a risk factor for cardiovascular diseases, and as a significant economic burden in our society, the question of whether cannabis use is associated with increased risk of diabetes is important. Included in this review are the assessments of three studies of cannabis use and metabolic dysregulation/metabolic syndrome, one study of cannabis use and prediabetes, and three studies of cannabis use and diabetes.

Is There an Association Between Cannabis Use and Metabolic Dysregulation, Metabolic Syndrome, Prediabetes, or Diabetes Mellitus?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis and metabolic dysregulation, metabolic syndrome, prediabetes, or diabetes mellitus. A review by Sidney (2016), published after the cutoff date for literature considered in this report, informed the discussion regarding the studies described in this section.

Primary Studies

Metabolic Dysregulation and Metabolic Syndrome Three cross-sectional studies were conducted using data from the National Health and Nutrition Examination Survey (NHANES) to examine the associations between cannabis use and glucose, insulin, and insulin resistance (Penner et al., 2013); cannabis use and the metabolic syndrome (Vidot et al., 2016); and cannabis use and tobacco cigarette smoking with metabolic syndrome (Yankey et al., 2016).

The study by Penner et al. (2013) included 4,657 NHANES participants from three exams conducted from 2005 to 2010 who were categorized as current, former, or never users of cannabis. The fasting mean glucose levels were not found to be significantly different in current users than in never users according to multivariable analyses that adjusted for age, sex, race/ethnicity, income, marital status, tobacco use, alcohol use,

BMI, and physical activity. Hemoglobin A1c did not vary by cannabis use status, while fasting insulin and homeostasis models of insulin resistance (HOMA-IR) were about 12 percent lower in current cannabis users than in never users. A study by Vidot et al. (2016) of 8,478 NHANES participants from three exams conducted from 2005 to 2010 found that the odds of metabolic syndrome were lower in current users than in never users, with an OR of 0.69 (95% CI = 0.47–1.00) according to a multivariable analysis that adjusted for age, sex, race/ethnicity, poverty-to-income ratio, tobacco smoking, and exam cycle year. Yankey et al. (2016) studied the association between cannabis and cigarette smoking with the prevalence of metabolic syndrome, using data from 3,051 2011–2012 NHANES participants. Compared with findings from respondents who reported never having used cannabis, regular use of cannabis (defined as smoking cannabis or hashish at least once per month for more than 1 year) was associated with reduced odds for metabolic syndrome (OR, 0.23; 95% CI = 0.06–0.90). The multivariable analysis controlled for age, education, family-income-to-poverty ratio, sex, medical insurance, marital status, tobacco smoking, physical activity, other drug use, and rehabilitation.

Prediabetes Bancks et al. (2015) examined the association of self-reported cannabis use with both the prevalence and the incidence of prediabetes in the Coronary Artery Risk Development in Young Adults (CARDIA) study. A cross-sectional analysis for diabetes was conducted in 3,024 participants at the Year 25 exam. Cannabis use was assessed by self-administered questions. Prediabetes was defined according to American Diabetes Association criteria and was present in 45 percent of participants. Relative to never use, the current use of cannabis was associated with an OR for prediabetes of 1.65 (95% CI = 1.15–2.38), and lifetime cannabis use of at least 100 times was associated with an OR of 1.49 (95% CI = 1.06–2.11). The multivariable analysis adjusted for age, sex, race, tobacco smoking, alcohol use, education, field center, systolic blood pressure, C-reactive protein (CRP), physical activity, and the use of other illicit drugs. The CARDIA longitudinal analysis examined the association of self-reported cannabis use at the Year 7 follow-up exam to incident prediabetes (51 percent of participants) at the four subsequent follow-up examinations, with an average of 13.8 years of follow-up. The adjusted hazard ratio (HR) for prediabetes associated with lifetime use of at least 100 times relative to never use of cannabis was 1.39 (95% CI = 1.13–1.71).

Diabetes Bancks et al. (2015) also examined the association of self-reported cannabis use and diabetes in both cross-sectional and longitudinal analyses conducted in the CARDIA study. The study population was the same for the cross-sectional analysis, and the adjustment variables

were the same as described for the prediabetes analysis. Diabetes was present in 11.8 percent of Year 25 exam participants. The ORs for diabetes were 1.18 (95% CI = 0.67–2.10) for current use and 1.42 (95% CI = 0.85–2.38) for lifetime use of at least 100 times relative to never use of cannabis. The longitudinal analysis examined the association between Year 7 exam and self-reported cannabis use to incident diabetes (11.1 percent of participants) at the four subsequent follow-up examinations (years 10, 15, 20, and 25). Relative to never use, the HR associated with diabetes for lifetime use of at least 100 times was 1.10 (95% CI = 0.74–1.64), adjusted for the same variables as the longitudinal analysis of prediabetes.

Two cross-sectional studies were conducted using data from the NHANES to examine the association of cannabis use with diabetes (Alshaarawy and Anthony, 2015; Rajavashisth et al., 2012). The first study (Rajavashisth et al., 2012) used interviewer-administered data regarding cannabis use and diabetes collected from 10,896 adults, ages 20 to 29 years, during NHANES III, conducted from 1988 to 1994. Relative to non-users, the OR for diabetes associated with current and past cannabis use was 0.36 (95% CI = 0.24–0.55), adjusted for race/ethnicity, physical activity, alcohol use, alcohol \times cannabis use interaction, BMI, total cholesterol, triglyceride, CRP, and hypertension.

In the second study, Alshaarawy and Anthony (2015) examined the association of cannabis use with diabetes in eight different replication samples and in a meta-analysis. The samples were obtained from four NHANES surveys (2005–2006, 2007–2008, 2009–2010, 2011–2012) and from a survey performed for the National Survey on Drug Use and Health (NSDUH) during the same time periods. A composite indicator of diabetes from the NHANES data combined interview reports of diabetes, current use of insulin and/or oral hypoglycemic medication, and lab-derived glycohemoglobin. Self-report of cannabis was assessed from the NSDUH surveys. Compared to nonusers, the adjusted odds ratios (aORs) for diabetes associated with current cannabis use ranged from 0.4 to 0.9, with a meta-analytic OR summary of 0.7 (95% CI = 0.6–0.8). Meta-analytic summary analyses performed within cigarette smoking strata found aORs were 0.8 (95% CI = 0.5–1.2) in respondents who reported never having smoked cigarettes and 0.8 (95% CI = 0.6–1.0) in current smokers.

Discussion of Findings

Overall, the articles reviewed by the committee were judged to be of good to fair quality for assessing the risk of metabolic dysregulation, metabolic syndrome, prediabetes, or diabetes mellitus associated with cannabis use. In their review of the evidence, the committee found that cannabis use had either an inverse association or no association with

BMI, an inverse association with metabolic dysregulation and metabolic syndrome, and an inverse association or no association with diabetes mellitus. The only study showing an increased risk was the prediabetes portion of the CARDIA study analysis.

As noted earlier, these are counterintuitive findings because THC tends to stimulate appetite, promote fat deposition, and promote adipogenesis. Potential explanations include the following:

- Cross-sectional studies do not allow one to assess temporality between exposure and outcome. With the exception of the longitudinal findings reported in the CARDIA study, all of the reported findings were from cross-sectional analyses.
- Dose estimates of cannabis exposure were generally imprecise and lacking information on cannabis strength, dose, frequency of use, and duration of use, although this may be because the cumulative dose for most cannabis users is not high enough to affect fat and glucose-insulin metabolism. Statistical confounders may exist in these studies which are not adequately controlled for by standard multivariable modeling. For example, in general, high levels of cannabis use are strongly associated with younger age, which is inversely associated with the incidence and prevalence of diabetes. They are also associated with tobacco cigarette smoking, a known risk factor for diabetes (Willi et al., 2007). Cannabis use was associated with increases in physical activity in the CARDIA study (Bancks et al., 2015) and in one of the NHANES studies (Rajavashisth et al., 2012). Physical activity is protective against obesity and diabetes.
- Reverse causality might result in a chronic illness such as diabetes leading to the cessation of potentially unhealthy habits, including cannabis use. This might help to explain why cannabis use is associated with prediabetes but not with diabetes.

CONCLUSION 6-3

6-3(a) There is limited evidence of a statistical association between cannabis use and decreased risk of metabolic syndrome and diabetes.

6-3(b) There is limited evidence of a statistical association between cannabis use and increased risk of prediabetes.

RESEARCH GAPS

The major gaps and opportunities relate to the paucity of longitudinal data for all of the cardiometabolic disorders and to the lack of data on the impact of cannabis use on risk in the older-adults age groups in which the majority of cardiovascular endpoints (e.g., acute myocardial infarction, stroke) occur. To address research gaps the committee suggests the following:

- Establishing a population cohort(s) in which cannabis use is regularly evaluated with standardized questionnaires accounting for the type of preparation, THC/other cannabinoid strength, the amount smoked or consumed, assessment of frequency and duration of use, and other cardiovascular disease (CVD) risk data, and in which researchers collect medical record and toxicology data or other biological marker data for cannabis use on incident CVD events.
- The cohort(s) need to be large enough that the association of cannabis with CVD events in the presence of potential statistical confounding variables (e.g., tobacco use, physical activity) can be validly assessed.
- Promote the collection of cannabis use data in electronic health records.

An additional suggestion is that basic research needs to be carried out to better understand the mechanisms for the role of cannabis as a possible trigger of AMI.

SUMMARY

This chapter summarizes the good and fair cardiometabolic literature published since 1999. The committee found limited evidence of an association between acute cannabis use—but not chronic cannabis use—and AMI risk. The committee also determined that there is limited evidence of an association between cannabis use and an increased risk of ischemic stroke or subarachnoid hemorrhage and also prediabetes and an association between cannabis and a decreased risk of metabolic dysregulation, metabolic syndrome, and diabetes. The limitations of the reviewed studies include a lack of information on different routes of cannabis administration (e.g., smoked, edible, etc.), a lack of adequate dose information, insufficient information on potential additives or contaminants, and inadequate data on total lifetime duration/dose of cannabis use. The committee has formed a number of research conclusions related to these health endpoints; however, it is important that each of these conclusions be

BOX 6-1
Summary of Chapter Conclusions*

There is limited evidence of a statistical association between cannabis use and:

- The triggering of acute myocardial infarction (cannabis smoking) (6-1a)
- Ischemic stroke or subarachnoid hemorrhage (6-2)
- Decreased risk of metabolic syndrome and diabetes (6-3a)
- Increased risk of prediabetes (6-3b)

There is no evidence to support or refute a statistical association between chronic effects of cannabis use and:

- The increased risk of acute myocardial infarction (6-1b)

* Numbers in parentheses correspond to chapter conclusion numbers.

interpreted within the context of the limitations discussed in the Discussion of Findings sections. Box 6-1 contains a summary of the conclusions for this chapter.

REFERENCES

- Alshaarawy, O., and J. C. Anthony. 2015. Cannabis smoking and diabetes mellitus: Results from meta-analysis with eight independent replication samples. *Epidemiology* 26(4):597–600.
- Aronow, W. S., and J. Cassidy. 1974. Effect of marihuana and placebo-marihuana smoking on angina pectoris. *New England Journal of Medicine* 291(2):65–67.
- Azofeifa, A., M. E. Mattson, G. Schauer, T. McAfee, A. Grant, and R. Lyerla. 2016. National estimates of marijuana use and related indicators—National Survey on Drug Use and Health, United States, 2002–2014. *Morbidity and Mortality Weekly Report Surveillance Summaries* 65(11):1–25.
- Bancks, M. P., M. J. Pletcher, S. G. Kertesz, S. Sidney, J. S. Rana, and P. J. Schreiner. 2015. Marijuana use and risk of prediabetes and diabetes by middle adulthood: The Coronary Artery Risk Development in Young Adults (CARDIA) study. *Diabetologia* 58(12):2736–2744.
- Barber, P. A., H. M. Pridmore, V. Krishnamurthy, S. Roberts, D. A. Spriggs, K. N. Carter, and N. E. Anderson. 2013. Cannabis, ischemic stroke, and transient ischemic attack: A case-control study. *Stroke* 44(8):2327–2329.
- Beaconsfield, P., J. Ginsburg, and R. Rainsbury. 1972. Marihuana smoking. Cardiovascular effects in man and possible mechanisms. *New England Journal of Medicine* 287(5):209–212.
- Benowitz, N. L., and R. T. Jones. 1981. Cardiovascular and metabolic considerations in prolonged cannabinoid administration in man. *Journal of Clinical Pharmacology* 21(8–9 Suppl):214S–223S.

- CDC (Centers for Disease Control and Prevention). 2014a. *National diabetes statistics report: Estimates of diabetes and its burden in the United States, 2014*. Atlanta, GA: U.S. Department of Health and Human Services.
- CDC. 2014b. Division of Diabetes Translation: National Diabetes Surveillance System. Long-term trends in diabetes. https://www.cdc.gov/diabetes/statistics/slides/long_term_trends.pdf. (accessed October 25, 2016).
- CDC. 2015. Annual number (in thousands) of new cases of diagnosed diabetes among adults aged 18–79 years, United States, 1980–2014. <http://www.cdc.gov/diabetes/statistics/incidence/fig1.htm> (accessed October 25, 2016).
- Di Marzo, V., F. Piscitelli, and R. Mechoulam. 2011. Cannabinoids and endocannabinoids in metabolic disorders with focus on diabetes. *Handbook of Experimental Pharmacology* 203:75–104.
- Flegal, K. M., M. D. Carroll, C. L. Ogden, and C. L. Johnson. 2002. Prevalence and trends in obesity among U.S. adults, 1999–2000. *JAMA* 288(14):1723–1727.
- Franz, C. A., and W. H. Frishman. 2016. Marijuana use and cardiovascular disease. *Cardiology in Review* 24(4):158–162.
- Gorelick, D. A., R. S. Goodwin, E. Schwilke, D. M. Schwoppe, W. D. Darwin, D. L. Kelly, R. P. McMahon, F. Liu, C. Ortemann-Renon, D. Bonnet, and M. A. Huestis. 2013. Tolerance to effects of high-dose oral Δ^9 -tetrahydrocannabinol and plasma cannabinoid concentrations in male daily cannabis smokers. *Journal of Analytical Toxicology* 37(1):11–16.
- Hayatbakhsh, M. R., M. J. O’Callaghan, A. A. Mamun, G. M. Williams, A. Clavarino, and J. M. Najman. 2010. Cannabis use and obesity and young adults. *American Journal of Drug and Alcohol Abuse* 36(6):350–356.
- Herning, R. I., W. E. Better, K. Tate, and J. L. Cadet. 2001. Marijuana abusers are at increased risk for stroke. Preliminary evidence from cerebrovascular perfusion data. *Annals of the New York Academy of Sciences* 939:413–415.
- IOM (Institute of Medicine). 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC: National Academy Press.
- Jamal, A., D. M. Homa, E. O’Connor, S. D. Babb, R. S. Caraballo, T. Singh, S. S. Hu, and B. A. King. 2015. Current Cigarette Smoking Among Adults—United States, 2005–2014. *Morbidity and Mortality Weekly Report* 64(44):1233–1240.
- Khiabani, H. Z., J. Mørland, and J. G. Bramness. 2008. Frequency and irregularity of heart rate in drivers suspected of driving under the influence of cannabis. *European Journal of Internal Medicine* 19:608–612.
- Kliil-Drori, A. J., L. Azoulay, and M. N. Pollak. 2016. Cancer, obesity, diabetes, and antidiabetic drugs: Is the fog clearing? *Nature Reviews: Clinical Oncology* August. doi:10.1038/nrclinonc.2016.120.
- Kochanek, K. D., S. L. Murphy, J. Q. Xu, and B. Tejada-Vera. 2016. Deaths: Final data for 2014. *National Vital Statistics Reports* 65(4):1–121. Hyattsville, MD: National Center for Health Statistics.
- Le Strat, Y., and B. Le Foll. 2011. Obesity and cannabis use: Results from 2 representative national surveys. *American Journal of Epidemiology* 174(8):929–933.
- Mittleman, M. A., R. A. Lewis, M. Maclure, J. B. Sherwood, and J. E. Muller. 2001. Triggering myocardial infarction by marijuana. *Circulation* 103(23):2805–2809.
- Mozaffarian, D., E. J. Benjamin, A. S. Go, D. K. Arnett, M. J. Blaha, M. Cushman, S. R. Das, S. de Ferranti, J. P. Després, H. J. Fullerton, V. J. Howard, M. D. Huffman, C. R. Isasi, M. C. Jiménez, S. E. Judd, B. M. Kissela, J. H. Lichtman, L. D. Lisabeth, S. Liu, R. H. Mackey, D. J. Magid, D. K. McGuire, E. R. Mohler, 3rd, C. S. Moy, P. Muntner, M. E. Mussolino, K. Nasir, R. W. Neumar, G. Nichol, L. Palaniappan, D. K. Pandey, M. J. Reeves, C. J. Rodriguez, W. Rosamond, P. D. Sorlie, J. Stein, A. Towfighi, T. N. Turan, S. S. Virani, D. Woo, R. W. Yeh, M. B. Turner; American Heart Association Statistics Committee, and Stroke Statistics Subcommittee. 2016. Heart disease and stroke statistics—2016 update: A report from the American Heart Association. *Circulation* 133(4):e38–e360.

- Ogden, C. L., M. D. Carroll, B. K. Kit, and K. M. Flegal. 2014. Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA* 311(8):806–814.
- Penner, E. A., H. Buettner, and M. A. Mittleman. 2013. The impact of marijuana use on glucose, insulin, and insulin resistance among U.S. adults. *American Journal of Medicine* 126(7):583–589.
- Phillips, M. C., J. M. Leyden, W. K. Chong, T. Kleinig, P. Czapran, A. Lee, S. A. Koblar, J. Jannes. 2011. Ischaemic stroke among young people aged 15 to 50 years in Adelaide, South Australia. *Medical Journal of Australia* 195(10):610–614.
- Rajavashisth, T. B., M. Shaheen, K. C. Norris, D. Pan, S. K. Sinha, J. Ortega, and T. C. Friedman. 2012. Decreased prevalence of diabetes in marijuana users: Cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) III. *BMJ Open* 2:e000494.
- Renaud, A. M., and Y. Cormier. 1986. Acute effects of marihuana smoking on maximal exercise performance. *Medicine and Science in Sports and Exercise* 18(6):685–689.
- Rodondi, N., M. J. Pletcher, K. Liu, S. B. Hulley, S. Sidney, and Coronary Artery Risk Development in Young Adults (CARDIA) Study. 2006. Marijuana use, diet, body mass index, and cardiovascular risk factors (from the CARDIA study). *American Journal of Cardiology* 98(4):478–484.
- Rumalla, K., A. Y. Reddy, and M. K. Mittal. 2016a. Recreational marijuana use and acute ischemic stroke: A population-based analysis of hospitalized patients in the United States. *Journal of Neurological Sciences* 364:191–196.
- Rumalla, K., A. Y. Reddy, and M. K. Mittal. 2016b. Association of recreational marijuana use with aneurysmal subarachnoid hemorrhage. *Journal of Stroke and Cerebrovascular Disease* 25(2):452–460.
- Sidney, S. 2002. Cardiovascular consequences of marijuana use. *Journal of Clinical Pharmacology* 42(11 Suppl):64S–70S.
- Sidney, S. 2016. Marijuana use and type 2 diabetes mellitus: A review. *Current Diabetes Reports* 16(11):117.
- Sidney, S., J. E. Beck, I. S. Tekawa, C. P. Quesenberry, and G. D. Friedman. 1997. Marijuana use and mortality. *American Journal of Public Health* 87(4):585–590.
- Smit, E., and C. J. Crespo. 2001. Dietary intake and nutritional status of U.S. adult marijuana users: Results from the Third National Health and Nutrition Examination Survey. *Public Health Nutrition* 4(3):781–786.
- Thomas, G., R. A. Kloner, and S. Rezkalla. 2014. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: What cardiologists need to know. *American Journal of Cardiology* 113(1):187–190.
- Vidot, D. C., G. Prado, W. M. Hlaing, H. J. Florez, K. L. Arheart, and S. E. Messiah. 2016. Metabolic syndrome among marijuana users in the United States: An analysis of National Health and Nutrition Examination survey data. *American Journal of Medicine* 129(2):173–179.
- Wang, X., R. Derakhshandeh, J. Liu, S. Narayan, P. Nabavizadeh, S. Le, O. M. Danforth, K. Pinnamaneni, H. J. Rodriguez, E. Luu, R. E. Sievers, S. F. Schick, S. A. Glantz, and M. L. Springer. 2016. One minute of marijuana secondhand smoke exposure substantially impairs vascular endothelial function. *Journal of the American Heart Association* 5(8):e003858.
- Warren, M., K. Frost-Pineda, and M. Gold. 2005. Body mass index and marijuana use. *Journal of Addictive Diseases* 24(3):95–100.
- Westover, A. N., S. McBride, and R. W. Haley. 2007. Stroke in young adults who abuse amphetamines or cocaine: A population-based study of hospitalized patients. *Archives of General Psychiatry* 64(4):495–502.
- Willi, C., P. Bodenmann, W. A. Ghali, P. D. Faris, and J. Cornuz. 2007. Active smoking and the risk of type 2 diabetes: A systematic review and meta-analysis. *JAMA* 298(22):2654–2664.

- Wolff, V., V. Lauer, O. Rouyer, F. Sellal, N. Meyer, J. S. Raul, C. Sabourdy, F. Boujan, C. Jahn, R. Beaujeux, and C. Marescaux. 2011. Cannabis use, ischemic stroke, and multifocal intracranial vasoconstriction: A prospective study in 48 consecutive young patients. *Stroke* 42(6):1778–1780.
- Wolff, V., J. P. Armspach, V. Lauer, O. Rouyer, M. Bataillard, C. Marescaux, and B. Gény. 2013. Cannabis-related stroke: Myth or reality? *Stroke* 44(2):558–563.
- Wolff, V., J. P. Armspach, V. Lauer, O. Rouyer, A. Ducros, C. Marescaux, and B. Gény. 2015. Ischaemic strokes with reversible vasoconstriction and without thunderclap headache: A variant of the reversible cerebral vasoconstriction syndrome? *Cerebrovascular Disease* 39(1):31–38.
- Yankey, B. N., S. Strasser, and I. S. Okosun. 2016. A cross-sectional analysis of the association between marijuana and cigarette smoking with metabolic syndrome among adults in the United States. *Diabetes and Metabolic Syndrome* 10(2 Suppl 1):S89–S95.

7

Respiratory Disease

Chapter Highlights

- Smoking cannabis on a regular basis is associated with chronic cough and phlegm production.
- Quitting cannabis smoking is likely to reduce chronic cough and phlegm production.
- It is unclear whether cannabis use is associated with chronic obstructive pulmonary disorder, asthma, or worsened lung function.

Environmental exposures are the leading causes of respiratory disease worldwide. Exposures to tobacco smoke and household air pollution consistently rank among the top risk factors not only for respiratory disease burden but also for the global burden of disease (Lim et al., 2012). Less is known, however, about the attributable effects of cannabis use on respiratory disease despite shared similarities with that of cigarette use and the fact that cannabis is the most commonly used inhaled drug in the United States after tobacco, with an estimated 22.2 million people ages 12 years and older reporting current use (CBHSQ, 2015). Moreover, it is estimated that more than 40 percent of current users smoke cannabis on a daily or near daily basis (Douglas et al., 2015). Given the known relationships between tobacco smoking and multiple respiratory conditions, one could hypothesize that long-term cannabis smoking leads to similar deleterious

effects on respiratory health, and some investigators argue that cannabis smoking may be even more harmful than that of tobacco smoking. Indeed, data collected from 15 volunteers suggest that smoking one cannabis joint can lead to four times the exposure to carbon monoxide and three to five times more tar deposition than smoking a single cigarette (Wu et al., 1988). This may be, in part, because cannabis smokers generally inhale more deeply and hold their breath for longer than do cigarette smokers (Wu et al., 1988) and because cannabis cigarettes do not commonly have filters as tobacco cigarettes often do. On the other hand, cannabis cigarettes are not as densely packed as tobacco cigarettes (Aldington et al., 2008), and cannabis users usually smoke fewer cannabis cigarettes per day than tobacco users smoke tobacco cigarettes per day.

The committee responsible for the 1999 Institute of Medicine (IOM) report *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999, p. 6) concluded that cannabis smoking was an important risk factor in the development of respiratory disease and recommended that “studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent.” The literature search conducted by the current committee did not identify any fair- or good-quality systematic reviews for cannabis use and respiratory disease published since 2011 (the cutoff established by the current committee); however, the committee identified—and elected to include—a systematic review by Tetrault et al. (2007) that provides a detailed synthesis of the available literature through 2005. A review by Tashkin (2013) and a position statement by Douglas et al. (2015), which summarized current evidence of the link between cannabis smoking and respiratory disease, were also considered by the committee. Fourteen primary articles published since 1999 that were not included in the systematic review from Tetrault et al. (2007) provided additional evidence on the association between smoking cannabis and respiratory diseases (Aldington et al., 2007; Bechtold et al., 2015; Hancox et al., 2010, 2015; Kempker et al., 2015; Macleod et al., 2015; Papatheodorou et al., 2016; Pletcher et al., 2012; Tan et al., 2009; Tashkin et al., 2012; Van Dam and Earleywine, 2010; Walden and Earleywine, 2008; Weekes et al., 2011; Yadavilli et al., 2014).

PULMONARY FUNCTION

Pulmonary function refers to lung size and function. Common measures of pulmonary function include forced expiratory volumes, lung volumes, airways resistance and conductance, and the diffusion capacity of the lung for carbon monoxide (DLCO). Spirometry values include the measurements of forced expiratory volumes, including forced expiratory

volume at 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC . The latter is a measure of airflow obstruction and, when combined with bronchodilator therapy, is used in the diagnosis of chronic obstructive pulmonary disorder (COPD).

Is There an Association Between Cannabis Use and Pulmonary Function?

Systematic Reviews

Tetrault et al. (2007) systematically reviewed the evidence found in 34 publications, of which 12 reported on the effects of airway response and 14 reported on the effects of pulmonary function. The authors found that short-term exposure to cannabis smoking resulted in bronchodilation. Specifically, acute cannabis smoking was consistently associated with improvements in specific airway conductance, peak flow measurements, and FEV_1 , as well as reversed bronchospasm from challenges by either methacholine or exercise. Any short-term benefits, however, were offset by the effects of long-term cannabis smoking. Specifically, regular cannabis smoking was associated with a lower specific airway conductance on average by 16 percent and also with a lower FEV_1 . There was also a dose-response effect between average daily quantity of cannabis and a lower specific airway conductance. However, the clinical significance of the association between regular cannabis smoking and a lower specific airways conductance is not known. Other studies that examined the association between long-term cannabis smoke exposure and pulmonary function have inconsistently found lower or no change in FEV_1 , FVC, FEV_1/FVC , DLCO, and airway hyperresponsiveness (Tetrault et al., 2007).

Primary Studies

Aldington et al. (2007) examined the cross-sectional relationship between long-term cannabis smoking and pulmonary function in a convenience sample of 339 participants in the Wellington Research Study. The inclusion criteria for cannabis and tobacco smokers were a lifetime exposure of at least 5 joint-years of cannabis (defined as smoking 1 joint per day for 1 year) or at least 1 pack-year of tobacco, respectively. Cannabis smoking was based on self-report. The researchers did not find an association between long-term cannabis smoking and pulmonary function variables. However, when cannabis smoking was analyzed in terms of joint-years, Aldington et al. (2007) found a significantly lower FEV_1/FVC , lower specific airways conductance, and a higher total lung capacity per joint-year smoked in cannabis smokers compared to nonsmokers. Based

on their analyses, the authors estimated that the negative association between each cannabis joint and a lower FEV_1/FVC was similar to that of 2.5 to 5 tobacco cigarettes. The committee identified a couple of problems with the analyses and the presentation of the results in the paper by Aldington et al. (2007). First, the authors reported main effects only from their analysis of covariance. A more conservative analysis would have considered the examination of interaction effects between cannabis smoke (or joint-years) and tobacco smoke (or pack-years) in a regression model to better dissect the contribution of cannabis smoke (or joint-years) versus tobacco smoke (or pack-years). Second, the authors incorrectly labeled the association with continuous measures of pulmonary function with cannabis smoke (or joint-years) as odds ratios (ORs) in tables 3 and 4; however, their methods correctly state that a multivariable analysis of covariance methods was used for continuous data.

Papatheodorou et al. (2016) analyzed cross-sectional data from 10,327 adults who participated in the National Health and Nutrition Examination Survey (NHANES) between 2007 and 2012. Cannabis smoking was based on self-report, but the researchers could not quantify joint-years. Cannabis smokers were categorized as never smokers ($n = 4,794$), past cannabis smokers ($n = 4,084$), cannabis smokers in the past 5–30 days ($n = 555$), and cannabis smokers in the past 0–4 days ($n = 891$). Current cannabis smokers were heavier tobacco smokers than were past and never smokers of cannabis, as measured by mean pack-years. In multivariable analyses, the investigators found that current smokers had a smaller FEV_1/FVC than never smokers (-0.01 and -0.02 , respectively), and they observed moderate to large increases in FEV_1 (49 mL and 89 mL, respectively) and FVC (159 mL and 204 mL, respectively) when comparing current smokers to never smokers. There was also an important decrease in exhaled nitric oxide among current smokers when compared to never smokers (-7 percent versus -14 percent), but it is unclear if this effect was confounded by the high prevalence of tobacco smoking in current cannabis users or if it represented a true decrease in exhaled nitric oxide due to cannabis smoking. The study by Papatheodorou et al. (2016) has some shortcomings. First, the researchers' analyses were based on cross-sectional data. Second, cannabis use was obtained by self-report and there may have been a bias of underreporting. Finally, there was a lack of data on the method of smoke inhalation and the frequency of cannabis smoking, thus not allowing for an analysis of the relationship between the frequency of cannabis use and pulmonary function.

Pletcher et al. (2012) analyzed longitudinal data from 5,115 adults in the Coronary Artery Risk Development in Young Adults (CARDIA) study and concluded that occasional and low cumulative cannabis smoking was not associated with adverse effects on pulmonary function. The

investigators noted that there was a trend toward decreases in FEV_1 over 20 years only in the heaviest cannabis smokers (≥ 20 joint-years). Similar to the findings of Papatheodorou et al. (2016), CARDIA investigators found a higher-than-expected FVC among all categories of cannabis smoking intensity. Despite the large sample size, the study by Pletcher et al. (2012) had a small number of heavy cannabis smokers. Other limitations include the risk of bias due to the self-reporting of cannabis use, a lack of data on the method of cannabis smoke inhalation, and bias due to unmeasured confounders as cannabis smoking was not the main objective of this study.

The study by Hancox et al. (2010) analyzed data of a cohort of 1,037 adult participants in Dunedin, New Zealand, followed longitudinally since childhood and asked about cannabis and tobacco use at ages 18, 21, 26, and 32 years. Cumulative exposure to cannabis was quantified as joint-years since age 17 years. Spirometry was conducted at 32 years. Cumulative cannabis use was associated with higher FVC, total lung capacity, and functional residual capacity and residual volume, but not with lower FEV_1 or FEV_1/FVC .

A small feasibility study by Van Dam and Earleywine (2010) found that the use of a cannabis vaporizer instead of smoking cannabis in 12 adult participants who did not develop a respiratory illness was associated with improvements in forced expiratory volumes at approximately 1 month after the introduction of the vaporizer; however, this study did not have a control group.

Discussion of Findings

Overall, acute cannabis smoking was associated with bronchodilation, but many of the authors agreed that any benefits may be offset when cannabis is smoked regularly. The current findings are inconclusive on a variety of pulmonary function measurements, and the findings may be affected by the quality of the studies, a failure to adjust for important confounders, including tobacco and other inhaled drugs, and other occupational and environmental exposures. The committee's findings are consistent with those reported in another recent review (Tashkin, 2013) and a position statement (Douglas et al., 2015).

The majority of studies, including those evaluated in the systematic review, relied on self-report for cannabis smoking. Many studies failed to control for tobacco smoking and occupational and other environmental exposures; did not control for the dose or duration of cannabis smoking; and did not use joint-years and instead based heavy cannabis smoking on having exceeded a specific threshold of joints. Even among studies that used joint-years, it is unclear how generalizable their findings are, given the potential high variability in lung-toxic content from joint to joint. Prior

studies have inconsistently documented decreases or no change in FEV_{1} , FEV_{1}/FVC , DLCO, and airway hyperresponsiveness. Moreover, neither the mechanism nor the clinical significance of the association between cannabis smoking and pulmonary function deficits is known beyond the possible impact of a high FVC in lowering the FEV_{1}/FVC ratio. While elevated lung volumes could be indicators of lung pathology, an elevated FVC by itself has not been associated with any lung pathology.

CONCLUSION 7-1

7-1(a) There is moderate evidence of a statistical association between cannabis smoking and improved airway dynamics with acute use, but not with chronic use.

7-1(b) There is moderate evidence of a statistical association between cannabis smoking and higher forced vital capacity (FVC).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is a clinical syndrome that consists of lower airway inflammation and damage that impairs airflow. Ranked as the fourth-leading cause of death worldwide by the World Health Organization, COPD has been estimated to cause more than 3 million deaths worldwide annually and has an estimated global prevalence of 10 percent in adults (Buist et al., 2007; Diaz-Guzman and Mannino, 2014). COPD is diagnosed with spirometry and is defined by a post-bronchodilator forced expiratory volume at 1 second divided by forced vital capacity (FEV_{1}/FVC) <70 percent (fixed cutoff) or as a post-bronchodilator FEV_{1}/FVC below the 5th percentile of a reference population (lower limit of normal). The committee responsible for *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999) suspected, but did not conclude, that chronic cannabis smoking causes COPD.

Is There an Association Between Cannabis Use and COPD?

Systematic Reviews

There is no discussion about the association between cannabis and COPD in the systematic review by Tetrault et al. (2007). In the position statement of the American Thoracic Society (Douglas et al., 2015), workshop members concluded that there was minimal impairment in occasional cannabis smokers when controlling for tobacco use. In con-

trast, there was a trend toward higher prevalence in heavier users based on studies of lung function decline (Pletcher et al., 2012; Tashkin et al., 1987); however, workshop members determined that this association was incompletely quantified.

Primary Studies

The study by Aldington et al. (2007) examined high-resolution computed tomography scans among the subgroups of participants with cannabis smoking only, cannabis and tobacco smoking, tobacco smoking only, and never smokers. They found inconsistent results: a decreased mean lung density, which is suggestive of emphysematous changes (mean percent of area below -950 Hounsfield units in three slices at 2.4 percent [95% confidence interval (CI) = 1.0%–3.8%] for cannabis smokers, but -0.6 percent [-2.0% – 0.8%] for tobacco smokers when compared to nonsmokers), but almost no evidence of macroscopic emphysema (1.3% versus 16.5% versus 18.5% versus 0% in cannabis-only smokers versus cannabis and tobacco smokers versus tobacco-only smokers versus non-smokers, respectively).

Tan et al. (2009) analyzed cross-sectional data collected in 878 adults ages 40 years and older from Vancouver, Canada, who participated in the Burden of Obstructive Lung Disease study on COPD prevalence. Current smoking of either tobacco or cannabis was defined as any smoking within the past year. Participants who had smoked at least 50 marijuana cigarettes but had no history of tobacco smoking were not at significantly greater risk of having COPD or more respiratory symptoms. There was inconsistent evidence for whether synergy from combined cannabis and tobacco smoking might affect the odds of having COPD or worse respiratory symptoms.

Specifically, the mean estimates for the tobacco and cannabis smoking versus tobacco-only smoking groups do not appear to be different, and the 95% CI for the tobacco and cannabis smoking group appears to overlap significantly with the tobacco-only smoking groups when evaluating either COPD or respiratory symptoms as the outcome.

Yadavilli et al. (2014) examined data from 709 participants over a 33-month period for hospital readmissions of COPD in illicit drug users and tobacco smokers. These investigators found that cannabis users had similar readmission rates to ex-tobacco or current tobacco users (mean readmissions at 0.22 versus 0.26) and much lower readmission rates than other illicit drug users (mean readmissions at 1.0). The unit for mean readmissions was not specified in either the tables or methods of this paper. The limitations of the study by Yadavilli et al. (2014) include a lack of spirometry data on all patients to confirm diagnosis of COPD, the self-

report of tobacco use, the risk for potential underreporting of illicit drug use, and the lack of outpatient visit frequency.

The study by Macleod et al. (2015) examined data from 500 adult participants, all of whom reported either tobacco smoking of ≥ 20 cigarettes per day for at least 5 years or cannabis of ≥ 1 joint per day for at least 1 year. There was no difference in the percent with COPD ($FEV_1/FVC < 0.7$) between tobacco-only users and tobacco and cannabis users (24.3 percent versus 25.2 percent; $p = 0.90$) for all ages or at any age group. Tobacco and cannabis users had more respiratory symptoms than did tobacco-only users (cough, phlegm, wheeze), but the investigators do not seem to report multivariable adjusted differences in the paper. The limitations of the study by Macleod et al. (2015) are that its cross-sectional design does not allow one to assess temporality between exposure and outcome, the lack of a nonsmoking group, the fact that its use of a convenience sample may have oversampled unwell participants, and the use of self-report for tobacco and cannabis.

Kempker et al. (2015) analyzed data from the 2007–2010 NHANES cohorts, similar to the work done by Papatheodorou et al. (2016). Kempker et al. (2015), however, also examined the information on cumulative lifetime use of cannabis available in the 2009–2010 NHANES cohort. Main findings were that 59 percent reported using cannabis at least once during their lifetime, and 12 percent reported use during the last month. When evaluating cumulative lifetime cannabis use, those with > 20 joint-years had a two times higher odds (OR, 2.1; 95% CI = 1.1–3.9) of having a pre-bronchodilator $FEV_1/FVC < 70$ percent than those with no cannabis exposure. However, as noted by others, cannabis use was associated with a higher FVC and no association with FEV_1 , which would spuriously reduce the ratio FEV_1/FVC . Beyond the limitations noted above for the paper by Papatheodorou et al. (2016), who also used NHANES data, the authors were limited to use pre-bronchodilator spirometry instead of using post-bronchodilator spirometry as commonly done in COPD studies.

Discussion of Findings

It is unclear whether regular cannabis use is associated with the risk of developing COPD or exacerbating COPD. Current studies may be confounded by tobacco smoking and the use of other inhaled drugs as well as by occupational and environmental exposures, and these studies have failed to quantify the effect of daily or near daily cannabis smoking on COPD risk and exacerbation. There is no evidence of physiological or imaging changes consistent with emphysema. The committee's findings are consistent with those of a recent position statement from the American Thoracic Society Marijuana Workgroup which concluded that there

was minimal impairment in light and occasional cannabis smokers when controlled for tobacco use and that the effects in heavy cannabis smokers remain poorly quantified (Douglas et al., 2015). The review by Tashkin (2013) concluded that the lack of evidence between cannabis use and longitudinal lung function decline (Pletcher et al., 2012) argues against the idea that smoking cannabis by itself is a risk factor for the development of COPD. This is further supported by the findings of Kempker et al. (2015), who concluded that smoking cannabis was not associated with lower FEV₁ after adjusting for tobacco smoking. However, smoking cannabis was associated with a higher FVC, which may have led to a spuriously lower FEV₁/FVC. Therefore, their analyses also do not support an association between heavy cannabis use (>20 lifetime joint-years) and obstruction on spirometry. The position statement by Douglas et al. (2015) concluded that the lack of solid epidemiologic association suggests that regular cannabis smoking may be a less significant risk factor for the development of COPD than tobacco smoking.

Cross-sectional studies are inadequate to establish temporality, and cohort studies of regular or daily cannabis users are a better design to help establish COPD risk over time. Better studies are needed to clearly separate the effects of cannabis smoking from those of tobacco smoking on COPD risk and COPD exacerbations, and better evidence is needed for heavy cannabis users.

CONCLUSION 7-2

7-2(a) There is limited evidence of a statistical association between occasional cannabis smoking and an increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use.

7-2(b) There is insufficient evidence to support or refute a statistical association between cannabis smoking and hospital admissions for COPD.

RESPIRATORY SYMPTOMS, INCLUDING CHRONIC BRONCHITIS

Respiratory symptoms include cough, phlegm, and wheeze. Chronic bronchitis is defined as chronic phlegm production or productive cough for 3 consecutive months per year for at least 2 consecutive years (Medical Research Council, 1965). Chronic bronchitis is a clinical diagnosis and does not require confirmation by spirometry or evidence of airflow obstruction. The committee responsible for *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999) concluded that acute and chronic bronchitis may occur as a result of chronic cannabis use.

Is There an Association Between Cannabis Use and Respiratory Symptoms, Including Chronic Bronchitis?

Systematic Reviews

The systematic review by Tetrault et al. (2007) summarized information from 14 studies that assessed the association between long-term cannabis smoking and respiratory symptoms. Nine of these studies were cross-sectional, 3 were case series, 1 was a case-control study, and 1 was a longitudinal cohort study. Data were relatively consistent in both cross-sectional and cohort studies in indicating that long-term cannabis smoking worsens respiratory symptoms, including cough (ORs, 1.7–2.0), increased sputum production (ORs, 1.5–1.9), and wheeze (ORs, 2.0–3.0). Other studies have reported effects on more episodes of acute bronchitis and pharyngitis, dyspnea, hoarse voice, worse cystic fibrosis symptoms, and chest tightness.

Primary Studies

Aldington et al. (2007) reported higher prevalence of wheeze (27 percent versus 11 percent), cough (29 percent versus 5 percent), chest tightness (49 percent versus 35 percent), and chronic bronchitis symptoms (19 percent versus 3 percent) among cannabis smokers than among non-smokers. There were no clear additive effects observed in the combined cannabis and tobacco smoking groups on respiratory symptoms.

Hancox et al. (2015) conducted a study in a cohort of 1,037 adults (52 percent male) in the Dunedin Multidisciplinary Health and Development Study. Cannabis and tobacco smoking histories were obtained at the ages of 18, 21, 26, 32, and 38 years. At each assessment, participants were asked how many times they had used cannabis in the previous year. Frequent cannabis users were defined as those who reported using marijuana ≥ 52 times over the previous year. Quitters were defined as a frequent cannabis user at the previous assessment but less than frequent at the current assessment. Because it was possible to quit frequent cannabis use more than once during the follow-up from 18 to 38 years of age, only the first recorded episode of quitting was used in analyses. In this study, the investigators found that frequent cannabis use was associated with morning cough (OR = 1.97, $p < 0.001$), sputum production (OR = 2.31, $p < 0.001$), and wheeze (OR = 1.55, $p < 0.001$), but not dyspnea ($p = 0.09$) (see Figure 7-1). Quitters (open triangles) also had fewer respiratory symptoms than those who did not quit (solid squares).

Limitations of the study by Hancox et al. (2015) include its reliance on self-reported data of cannabis use without objective confirmation, the

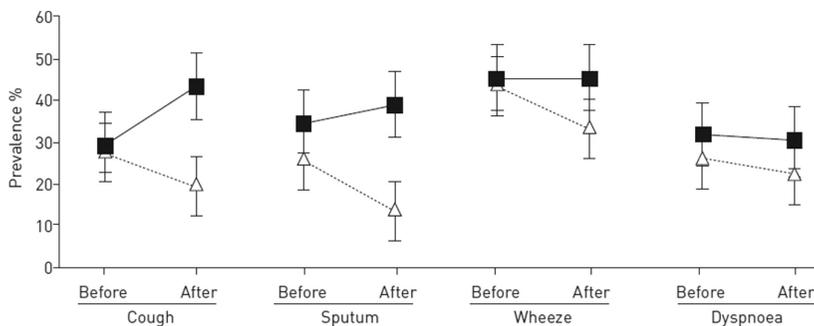


FIGURE 7-1 Prevalence of symptoms before and after quitting regular cannabis use (open triangles) and among those who used cannabis for two consecutive phases (solid squares). Vertical bars show 95% confidence level.

SOURCE: Hancox et al., 2015.

classification of nonusers as those with <52 times of cannabis use, and a lack of data as to whether cannabis use was specifically from smoking.

Walden and Earleywine (2008) conducted a cross-sectional Internet survey of 5,987 adults worldwide who used cannabis at least once per month. They quantified frequency, amount, and degree of usual and maximal intoxication, and they also asked about respiratory symptoms using a composite score produced from the answers to six standard questions about cough, morning phlegm, dyspnea, chest wheezing other than during colds, and nighttime awakenings because of chest tightness. They found that the frequency of use, the amount used (in quarter bags per month), and the degree of usual intoxication were all positively associated with more respiratory symptoms. Limitations for this study include its recruitment of participants from organizations that advocate drug policy reform, its reliance on self-reported data of cannabis or tobacco use without objective confirmation, and the lack of data about cannabis use for medical versus recreational purposes.

Tashkin et al. (2012) followed 299 participants from a longitudinal cohort study for at least two visits over 9.8 years and examined the relationship between symptoms for chronic bronchitis and cannabis use. They found that current cannabis users were more likely to have cough (OR = 1.7), sputum (OR = 2.1), increased bronchitis episodes (OR = 2.3), and wheeze (OR = 3.4) when compared to never users. They also found that current cannabis users were more likely to have cough (OR = 3.3), sputum (OR = 4.2), or wheeze (OR = 2.1) than former users. Similar to

the studies by Hancox et al. (2015) and Walden and Earleywine (2008), these findings demonstrated the benefit of cannabis smoking cessation in resolving preexisting symptoms of chronic bronchitis. The limitations of this study include its reliance on self-reported data of cannabis or tobacco use without objective confirmation and high rates of loss to follow-up or variable follow-up periods.

A small feasibility study by Van Dam and Earleywine (2010) of 12 adult participants who did not develop a respiratory illness during the trial found that the use of a cannabis vaporizer instead of smoking cannabis was correlated with the resolution of cannabis-related respiratory symptoms at approximately 1 month after the introduction of the vaporizer; however, this study did not have a control group.

Discussion of Findings

Regular cannabis use was associated with airway injury, worsening respiratory symptoms, and more frequent chronic bronchitis episodes. There were no clear additive effects on respiratory symptoms observed from smoking both cannabis and tobacco. Cannabis smoking cessation was temporally associated with the resolution of chronic bronchitis symptoms, and a small feasibility study suggests that use of a vaporizer instead of smoking cannabis may lead to the resolution of respiratory symptoms. The committee's findings are consistent with those reported in a recent review (Tashkin, 2013) and position statement (Douglas et al., 2015).

The majority of studies relied on self-report for cannabis smoking. Many studies failed to control for tobacco, occupational, and other environmental exposures; did not control for the dose or duration of the cannabis smoke exposure; and did not use joint-years and instead based heavy cannabis exposure on exceeding a specific threshold of cigarettes. Even among studies that used joint-years, it is unclear how generalizable the findings are, given the potential high variability in tetrahydrocannabinol (THC) content from joint to joint and from year to year.

CONCLUSION 7-3

7-3(a) There is substantial evidence of a statistical association between long-term cannabis smoking and worse respiratory symptoms and more frequent chronic bronchitis episodes.

7-3(b) There is moderate evidence of a statistical association between cessation of cannabis smoking and improvements in respiratory symptoms.

ASTHMA

Asthma is a clinical syndrome that is associated with airways inflammation, airflow limitation, bronchial hyperresponsiveness, and symptoms of episodic wheeze and cough. It is predominantly an allergic disease. Worldwide, asthma is thought to affect 300 million people, and it is responsible for more disability-adjusted life-years lost than diabetes mellitus. Asthma was not specifically addressed in *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999).

Is There an Association Between Cannabis Use and Asthma?

Systematic Reviews

The systematic review by Tetrault et al. (2007) referred to only one study that described the association between cannabis use and asthma exacerbations. Upon retrieving this study, the committee found that this was a letter to the editor which reported findings of a case-control study of 100 participants ages 18–55 years, with and without asthma, admitted to the emergency department. In this study, the authors found no association between THC and asthma (Gaeta et al., 1996).

Primary Studies

Bechtold et al. (2015) reported on a follow-up of a cohort of boys who participated in the Pittsburgh Youth Study. A total of 506 boys were followed longitudinally: 257 scored at or above the 70th percentile of a multi-informant conduct problem score, and 249 scored below the 70th percentile. This study found no link between cannabis use and self-reported asthma symptoms. The limitations of this study include a lack of generalizability to the general population, given the selection criteria for conduct problems, a lack of inclusion of women in their study, and the fact that health outcomes were based on self-report and biased to those who had sought care for health problems.

Weekes et al. (2011) studied a cohort of 110 black urban adolescents with asthma. In this study, the investigators found that 16 percent of the adolescents smoked cannabis, but there was no association between cannabis use and asthma concern or asthma severity or asthma symptoms. The limitations of this study include the reliance on the self-report of cannabis use, which the study authors speculated may be underreported in black adolescents when compared to whites, and a lack of data on asthma medication adherence.

Discussion of Findings

The committee did not find evidence for an association between cannabis use and either asthma risk or asthma exacerbations, and current studies failed to control for other important confounders, including adherence to asthma medications.

The evidence linking cannabis use with asthma risk or exacerbation is limited by the scope and sample size of available studies and by the use of more standardized approaches to measure asthma prevalence or exacerbations of asthma. Few studies have examined the link between cannabis and asthma, and no clear evidence exists of a link between asthma or asthma exacerbation and cannabis use. However, asthma symptoms such as wheeze appear to be common among cannabis users.

CONCLUSION 7-4 There is no or insufficient evidence to support or refute a statistical association between cannabis smoking and asthma development or asthma exacerbation.

RESEARCH GAPS

The effects of cannabis smoke on respiratory health remain poorly quantified. Further research is needed to better elucidate the influence of exposure levels to cannabis smoke on respiratory outcomes, the chronicity of cannabis smoking, the effects of an underlying predisposition to respiratory disease, and possible interaction effects with tobacco smoke to promote airway inflammation, worsen respiratory symptoms, accelerate lung function decline, or increase exacerbation of COPD and asthma. Previous studies have not been able to adequately separate cannabis smoke effects from tobacco smoke effects, and this has meant that some important questions remain unanswered. It is unknown whether or not:

- Long-term cannabis smoking, above and beyond that of tobacco smoking, leads to a more rapid decline in lung function and to the development of chronic bronchitis or COPD.
- Cannabis smoking increases the risk of allergic disease or asthma.
- Alternative inhaled delivery methods of cannabis result in fewer respiratory symptoms.

To address the research gaps relevant to respiratory disease, the committee suggests the following:

- Design better observational studies with both self-reported and quantitative measures of cannabis smoking and systematic approaches to measure the duration and dose to determine if

long-term exposure to cannabis smoke, above and beyond exposure to tobacco smoke, leads to the development of chronic bronchitis or COPD or to a higher rate of COPD exacerbation.

- Design longitudinal studies to determine if long-term cannabis smoking is associated with the development of allergic disease and risk of asthma.
- Conduct clinical trials of alternative inhaled delivery methods versus cannabis smoking to determine if they reduce respiratory symptoms.

SUMMARY

This chapter summarizes all of the respiratory disease literature that has been published since 1999 and deemed to be good or fair by the committee. Overall, the risks of respiratory complications of cannabis smoking appear to be relatively small and to be far lower than those of tobacco smoking. While heavy cannabis users may be at a higher risk for developing chronic bronchitis and COPD or at an increased risk of exacerbating COPD and asthma, current studies do not provide sufficient evidence for a link. Limitations of reviewed studies are that it is difficult to separate the effects of cannabis smoking from those of tobacco smoking from current available data; that exposures have generally been measured by self-report of cannabis smoking; and that there is a lack of cohort studies of regular or daily cannabis users, of adequate controls for environmental factors, and of generalizability of findings. The committee has formed a number of research conclusions related to these health endpoints (see Box 7-1); however, it is important that each of these conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections.

BOX 7-1
Summary of Chapter Conclusions*

There is substantial evidence of a statistical association between cannabis smoking and:

- Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term cannabis smoking) (7-3a)

There is moderate evidence of a statistical association between cannabis smoking and:

- Improved airway dynamics with acute use, but not with chronic use (7-1a)
- Higher forced vital capacity (FVC) (7-1b)

There is moderate evidence of a statistical association between *the cessation* of cannabis smoking and:

- Improvements in respiratory symptoms (7-3b)

There is limited evidence of a statistical association between cannabis smoking and:

- An increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use (occasional cannabis smoking) (7-2a)

There is no or insufficient evidence to support or refute a statistical association between cannabis smoking and:

- Hospital admissions for COPD (7-2b)
- Asthma development or asthma exacerbation (7-4)

* Numbers in parentheses correspond to chapter conclusion numbers.

REFERENCES

- Aldington, S., M. Williams, M. Nowitz, M. Weatherall, A. Pritchard, A. McNaughton, G. Robinson, and R. Beasley. 2007. Effects of cannabis on pulmonary structure, function and symptoms. *Thorax* 62:1058–1063.
- Aldington, S., M. Harwood, B. Cox, M. Weatherall, L. Beckert, A. Hansell, A. Pritchard, G. Robinson, R. Beasley; and the Cannabis and Respiratory Disease Research Group. 2008. Cannabis use and cancer of the head and neck: Case-control study. *Otolaryngology and Head and Neck Surgery* 138(3):374–380.

- Bechtold, J., T. Simpson, H. R. White, and D. Pardini. 2015. Chronic adolescent marijuana use as a risk factor for physical and mental health problems in young adult men. *Psychology and Addictive Behaviors* 29:552–563.
- Buist, A. S., M. A. McBurnie, W. M. Vollmer, S. Gillespie, P. Burney, D. M. Mannino, A. M. B. Menezes, S. D. Sullivan, T. A. Lee, K. B. Weiss, R. L. Jensen, G. B. Marks, A. Gulsvik, and E. Nizankowska-Mogilnicka. 2007. International variation in the prevalence of COPD (The BOLD study): A population-based prevalence study. *Lancet* 370:741–750.
- CBHSQ (Center for Behavioral Health Statistics and Quality). 2015. Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health (HHS Publication No. SMA 15-4927, NSDUH Series H-50).
- Diaz-Guzman, E., and D. M. Mannino. 2014. Epidemiology and prevalence of chronic obstructive pulmonary disease. *Clinics in Chest Medicine* 35(1):7–16.
- Douglas, I. S., T. E. Albertson, P. Folan, N. A. Hanania, D. P. Tashkin, D. J. Upson, and F. T. Leone. 2015. Implications of marijuana decriminalization on the practice of pulmonary, critical care, and sleep medicine. A report of the American Thoracic Society Marijuana Workgroup. *Annals of the American Thoracic Society* 12:1700–1710.
- Gaeta, T. J., R. Hammock, T. A. Spevack, H. Brown, and K. Rhoden. 1996. Association between substance abuse and acute exacerbation of bronchial asthma. *Academic Emergency Medicine* 3(12):1170–1172.
- Hancox, R. J., R. Poulton, M. Ely, D. Welch, D. R. Taylor, C. R. McLachlan, J. M. Greene, T. E. Moffitt, A. Caspi, and M. R. Sears. 2010. Effects of cannabis on lung function: a population-based cohort study. *The European Respiratory Journal* 35(1):42–47.
- Hancox, R. J., H. H. Shin, A. R. Gray, R. Poulton, and M. R. Sears. 2015. Effects of quitting cannabis on respiratory symptoms. *European Respiratory Journal* 46:80–87.
- IOM (Institute of Medicine). 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC: National Academy Press.
- Kempker, J. A., E. G. Honig, and G. Martin. 2015. The effects of marijuana exposure on respiratory health in U.S. adults. *Annals of the American Thoracic Society* 12:135–141.
- Lim, S. S., T. Vos, A. D. Flaxman, G. Danaei, K. Shibuya, H. Adair-Rohani, et al. 2012. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 380:2224–2260.
- Macleod, J., R. Robertson, L. Copeland, J. McKenzie, R. Elton, and P. Reid. 2015. Cannabis, tobacco smoking, and lung function: A cross-sectional observational study in a general practice population. *British Journal of General Practice* 65:e89–e95.
- Medical Research Council. 1965. Definition and classification of chronic bronchitis for clinical and epidemiological purposes. A report to the Medical Research Council by their Committee on the Aetiology of Chronic Bronchitis. *Lancet* 1:775–779.
- Papathodorou, S. I., H. Buettner, M. B. Rice, and M. A. Mittleman. 2016. Recent marijuana use and associations with exhaled nitric oxide and pulmonary function in adults in the United States. *Chest* 149:1428–1435.
- Pletcher, M. J., E. Vittinghoff, R. Kathan, J. Richman, M. Safford, S. Sidney, F. Lin, and S. Kertesz. 2012. Association between marijuana exposure and pulmonary function over 20 years. *JAMA* 307:173–181.
- Tan, W. C., C. Lo, A. Jong, L. Xing, M. J. Fitzgerald, W. M. Vollmer, S. A. Buist, and D. D. Sin. 2009. Vancouver Burden of Obstructive Lung Disease (BOLD) Research Group. Marijuana and chronic obstructive lung disease: A population-based study. *Canadian Medical Association Journal* 180:814–820.
- Tashkin, D. P. 2013. Effects of marijuana smoking on the lung. *Annals of the American Thoracic Society* 10:239–247.

- Tashkin, D. P., A. H. Coulson, V. A. Clark, M. Simmons, L. B. Bourque, S. Duann, G. H. Spivey, and H. Gong. 1987. Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. *American Review of Respiratory Disease* 135:209–216.
- Tashkin, D. P., M. S. Simmons, and C. H. Tseng. 2012. Impact of changes in regular use of marijuana and/or tobacco on chronic bronchitis. *COPD* 9:367–374.
- Tetrault, J. M., K. Crothers, B. A. Moore, R. Mehra, J. Concato, and D. A. Fiellin. 2007. Effects of marijuana smoking on pulmonary function and respiratory complications: A systematic review. *Archives of Internal Medicine* 167:221–228.
- Van Dam, N. T., and M. Earleywine. 2010. Pulmonary function in cannabis users: Support for a clinical trial of the vaporizer. *International Journal of Drug Policy* 21:511–513.
- Walden, N., and M. Earleywine. 2008. How high: Quantity as a predictor of cannabis-related problems. *Harm Reduction Journal* 5:20.
- Weekes, J. C., S. Cotton, and M. E. McGrady. 2011. Predictors of substance use among black urban adolescents with asthma: A longitudinal assessment. *Journal of the National Medical Association* 103:392–398.
- Wu, T. C., D. P. Tashkin, B. Djahed, and J. E. Rose. 1988. Pulmonary hazards of smoking marijuana as compared with tobacco. *New England Journal of Medicine* 318:347–351.
- Yadavilli, R., A. Collins, W. Y. Ding, N. Garner, J. Williams, and H. Burhan. 2014. Hospital readmissions with exacerbation of obstructive pulmonary disease in illicit drug smokers. *Lung* 192:669–673.

8

Immunity

Chapter Highlights

- There exists a paucity of data on the effects of cannabis or cannabinoid-based therapeutics on the human immune system.
- There is insufficient data to draw overarching conclusions concerning the effects of cannabis smoke or cannabinoids on immune competence.
- There is limited evidence to suggest that regular exposure to cannabis smoke may have anti-inflammatory activity.
- There is insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and adverse effects on immune status in individuals with HIV.

The immune system is composed of many different cells that perform a wide variety of functions in order to provide immunity against pathogens and other foreign bodies. Many assays and methods exist to evaluate specific components of the immune system and to assess changes in immune function and status. Toward this end, there is a sizable literature reporting on investigations into the effects of plant-derived, synthetic, and endogenous cannabinoids on various aspects of immune competence in experimental animals and in cell-based assays. The scientific literature is full of studies that used these animal- and cell-based immunological

approaches to show that cannabinoids modulate (either suppressing or enhancing) the functions of most of the types of immune cells that have been evaluated. By contrast, the investigations into the effects of cannabis or cannabinoid-based therapeutics on immunity in human subjects are quite limited.

The majority of studies investigating the association between cannabis or cannabinoid use and effects on human immunity have assessed one or more immunological parameters in patients infected with human immunodeficiency virus (HIV) or viral hepatitis C (HCV). For example, in the case of HIV patients, who are extensively studied within the context of cannabis exposure, these investigations have evaluated only a small number of immunological endpoints, the most common being the number of certain types of T cells (i.e., CD4⁺ and CD8⁺ T cells) in circulation and also the viral load. The limited measurements provide little information about the effect of cannabis use on overall immune status among individuals with HIV. Other studies have evaluated the effects of cannabis on immune endpoints in healthy individuals or on their susceptibility to infectious agents. In healthy individuals, these evaluations have focused primarily on the effects of cannabis use on circulating cytokines concentrations, principally inflammatory cytokines. Again, these examples emphasize the very limited and extremely narrow scope of assessments that have been conducted to examine the effects of cannabis on immune competence in humans to date.

This chapter reviews the current evidence on the association between cannabis use and immune competence in healthy populations and in individuals with infectious disease. Because the immune system plays a primary role in fighting and protecting against disease, the chapter will review evidence on the potential association between cannabis use and indicators of immune functioning as well as the potential association between cannabis use and susceptibility to, and progression of, infectious disease and cancer. Due to the paucity of human studies evaluating the effects of cannabis on the immune system, the committee identified no good- or fair-quality systematic reviews reporting on the health endpoints addressed in this chapter. Consequently, this chapter's conclusions are based on a review of 14 primary literature articles that best address the committee's research questions of interest. Study limitations and research gaps are noted, and the strength of the available evidence is weighed in five formal conclusions.

IMMUNE COMPETENCE

In several of the studies reviewed below, the effects of cannabis use on immune competence were assessed via direct measurement of specific

immune effect or functions in healthy individuals. The primary advantage of evaluating specific immune responses is that the immune system is composed of many different cell types, each of which performs several distinct functions. Assessing specific immune responses provides more information on whether, how, and to what extent an agent such as cannabis affects particular cells in the immune system. Although the perturbations in immune competence discussed in this section are not health effects in the sense used throughout this report, they may alter a person's susceptibility to infection or have broad effects on immune competence, and they are reviewed for that reason.

The challenge with this type of information is that it is difficult to ascertain whether a deficit in a specific immune function, unless extreme, necessarily results in greater susceptibility to infection by a pathogen. Conversely, it is difficult to extrapolate results showing enhanced immune responsiveness due to exposure to an agent and to determine whether that exposure may lead to an increased incidence of hypersensitivity or autoimmune disease. Therefore, the evaluation of immune competence requires a comprehensive assessment of a broad range of different cell types and their functions, which to date has not been conducted in cannabis users.

Is There an Association Between Cannabis Use and Immune Competence in Individuals Without an Infectious Disease?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and immune competence in individuals without an infectious disease.

Primary Literature

Keen and Turner (2015) evaluated the serum levels of two inflammatory cytokines, interleukin-1 alpha (IL-1 α) and tumor necrosis factor (TNF), in a total of 168 African American study participants of whom 46 were lifetime cannabis users and 77 did not use any illicit drugs. After adjusting for demographic and physiological variables, study participants who did not use illicit drugs were not significantly more likely to have higher background serum IL-1 α levels than lifetime cannabis users (odds ratio [OR], 0.77, 95% confidence interval [CI] = 0.34–1.74). By contrast, study participants who did not use illicit drugs were significantly more likely to have higher serum TNF levels than lifetime cannabis users (OR, 2.73, 95% CI = 1.18–6.31).

In another study, several immune parameters were evaluated in adult Egyptians (Abo-Elnazar et al., 2014). The study included 20 cannabis users and 10 controls with no history of drug abuse. CD4⁺ peripheral blood T cells from cannabis users showed a statistically significant decrease in proliferative response to mitogenic stimulation (phytohemagglutinin [PHA]) in culture as measured by the methyl thiazolyl tetrazolium (MTT) stimulation index when compared to CD4⁺ T cells from controls (mean = 1.14 ± 0.28 versus mean = 1.47 ± 0.35 , $p = 0.001$). Supernatants from these cultures were quantified for T cell cytokines; interleukin-10 (IL-10), which is an anti-inflammatory cytokine; and interleukin-17 (IL-17), which is a proinflammatory cytokine. When compared to CD4⁺ T cells from non-drug-using controls, CD4⁺ T cells from cannabis users showed an approximately 50 percent decrease in proinflammatory IL-17 ($129.05 \text{ pg/ml} \pm 44.24 \text{ pg/ml}$ versus $206.30 \text{ pg/ml} \pm 51.05 \text{ pg/ml}$, $p < 0.001$) and a two-fold increase in anti-inflammatory IL-10 (mean = $258.10 \text{ pg/ml} \pm 79.91 \text{ pg/ml}$ versus mean = $138.70 \text{ pg/ml} \pm 38.11 \text{ pg/ml}$, $p = 0.002$). A major limitation of Abo-Elnazar et al. (2014) is the very small number of study participants.

Pacifici et al. (2007) conducted a longitudinal study which included an evaluation of total leukocytes as well as the number of CD4⁺ T cells, CD8⁺ T cells, B cells, and natural killer (NK) cells at the beginning of the study and 12 months later in 34 healthy controls who had not used illicit drugs in the previous 12 months and in 23 study participants who were occasional or regular users of cannabis. There was a statistically significant difference between controls and cannabis-using study participants with respect to the number of NK cells at the initiation of the study (mean = $205.1 \text{ cells}/\mu\text{l} \pm 83.4 \text{ cells}/\mu\text{l}$ versus $126.1 \text{ cells}/\mu\text{l} \pm 80.0 \text{ cells}/\mu\text{l}$) or when evaluated at 12 months (mean = $196.8 \text{ cells}/\mu\text{l} \pm 79.3 \text{ cells}/\mu\text{l}$ versus mean = $101.7 \text{ cells}/\mu\text{l} \pm 48.5 \text{ cells}/\mu\text{l}$). By contrast, differences between controls and cannabis-using study participants in the number of CD4⁺ T cells, CD8⁺ T cells, and CD19 B cells were not statistically significant at the initiation of the study or 12 months later. In addition, PHA-induced proliferation, supernatant interleukin-2 (IL-2) (a measure of T cell function), and transforming growth factor beta 1 (TGF- β 1) (a proinflammatory cytokine) were assessed at the initiation of the study. Statistically significant differences were observed between controls and cannabis users in terms of PHA-induced proliferation (mean = $96.9\% \pm 15.6\%$ versus mean = $72.3\% \pm 32.1\%$) and the activity units per ml of IL-2 (mean = $10.7 \text{ U/ml} \pm 3.8 \text{ U/ml}$ versus mean = $6.3 \text{ U/ml} \pm 4.4 \text{ U/ml}$), whereas the difference between controls and cannabis users in the activity units per ml of TGF- β 1 was not statistically significant.

Jatoi et al. (2002) conducted a study involving 85 study participants with advanced cancer and weight loss to compare the effect of megestrol acetate (800 mg/day) and oral dronabinol tablets (2.5 mg twice daily),

separately and in combination, on levels of serum interleukin-6 (IL-6), a cytokine associated with anorexia and weight loss. There was no statistically significant change in serum IL-6 levels 1 month after study initiation among study participants receiving dronabinol alone (mean difference = $-0.62 \text{ pg/ml} \pm 3.5 \text{ pg/ml}$) or in combination with megestrol acetate (mean difference = $-0.2 \text{ pg/ml} \pm 3.1 \text{ pg/ml}$).

A longitudinal study followed study participants from birth to 38 years of age in order to investigate potential associations between cannabis use occurring between 18 and 38 years of age and physical health problems at 38 years of age, including systemic inflammation as measured by C-reactive protein levels (Meier et al., 2016). Among 947 study participants, there was no statistically significant association between joint-years of cannabis use and systemic inflammation after controlling for biological sex and tobacco use (β 0.00, 95% CI = -0.07 – 0.08). After controlling for biological sex, systemic inflammation at 26 years of age, and tobacco use, the association between joint-years of cannabis use and changes in systemic inflammation between 26 and 38 years of age was not statistically significant (β 0.05, 95% CI = -0.03 – 0.13).

Discussion of Findings

One trend that appeared to be supported by several studies was the observation that regular exposure to cannabis smoke decreased several regulatory factors that are secreted by leukocytes and that are well established in mediating inflammation. Consistent with the premise that cannabinoids may possess anti-inflammatory activity, one study showed an enhanced production of an anti-inflammatory mediator, which could be indicative of a decline in immune competence (Abo-Elnazar et al., 2014). By contrast, anti-inflammatory activity of cannabis, under certain conditions, could be beneficial because inflammation is a key event in the processes of many diseases. For example, chronic inflammation is believed to be central in HIV-associated neurocognitive disorders and anti-inflammatory activity of cannabis could potentially be beneficial in decreasing the progression of neurocognitive decline (Gill and Kolson, 2014). The finding that cannabinoids may possess anti-inflammatory activity is consistent with findings in studies conducted in experimental animal and in cell culture experiments (Klein, 2005).

The limitations of the studies conducted to date are numerous, with the most significant being the absence of a comprehensive evaluation of the effects of cannabis smoke on immune competence. In addition, several of the studies used a small number of study participants with very limited information on the study participants' level of exposure to cannabis. Based on the very limited evaluations of only a few immune parameters,

it is not possible to draw overarching conclusions concerning the effects of cannabis smoke or cannabinoids on immune competence.

CONCLUSION 8-1

8-1(a) There is limited evidence of a statistical association between cannabis smoking and a decrease in the production of several inflammatory cytokines in healthy individuals.

8-1(b) There is insufficient evidence to support or refute a statistical association between cannabis smoking and other adverse immune cell responses in healthy individuals.

SUSCEPTIBILITY TO AND PROGRESSION OF INFECTIOUS DISEASE

The primary role of the immune system is to protect against infectious agents (e.g., bacteria, viruses, parasites). The immune system confers this protection by its ability to recognize what is foreign, often termed as “non-self,” which it then seeks to destroy using a broad repertoire of different cell types and mechanisms. Significant changes in immune competence can result in serious adverse health effects. For example, inappropriate or exaggerated immune responses can result in autoimmunity or allergy. Conversely, the suppression of immune function can lead to an increased susceptibility to infectious agents, an increased duration of infection, or a reduced ability to recognize and destroy cancer cells. A large body of literature using animal models and cell cultures has described the immunosuppressive properties of cannabinoids. Reduced immune competence due to cannabis smoke or cannabinoid treatment would be especially relevant in cases when immunocompromised HIV patients used the cannabis to stimulate their appetite or cancer patients used it to relieve the nausea associated with cancer chemotherapeutic drugs. Very few studies have investigated the effects of cannabis smoke or cannabinoids on the susceptibility to, or clearance of, infectious agents or on progression of cancer in human subjects. This section discusses findings from the few studies that have evaluated the association between cannabis use and immune status in terms of an individual’s susceptibility to infection and the health status of individuals with HIV, HCV, and other infectious diseases.

Is There an Association Between Cannabis Use and Immune Status in Individuals with HIV?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and immune status in individuals with HIV.¹

Primary Literature

Several studies have been conducted with the specific objective of determining whether cannabis smoking or therapeutic dronabinol produces adverse effects on immune competence in HIV patients. In a prospective randomized controlled trial (RCT), 62 study participants ages 18 years and older who were infected with HIV were randomized to receive cannabis (up to three cigarettes daily), dronabinol (2.5 mg oral tablet three times daily), or an oral placebo over a 21-day period (Bredt et al., 2002). The change in absolute lymphocyte concentration among study participants receiving cannabis was statistically significantly greater than among study participants receiving the placebo (median change = 300 cells/ μ l versus 0.00 cells/ μ l, $p = 0.1$). As compared to study participants receiving the placebo, those receiving dronabinol experienced significantly greater changes in %CD8+CD38+HLA-DR+ cells (median change -3.50 versus 0.05 , $p = 0.001$) and in %CD8+CD69+ cells (median change -0.30 versus 0.05 , $p = 0.04$) during the study period. Bredt et al. (2002) state that these statistically significant changes “do not constitute [a] meaningful pattern of changes in immune phenotype of function” (Bredt et al., 2002, p. 87S).

By contrast, study participants in neither of the cannabinoid study arms experienced statistically significantly greater changes in lymphoproliferative responses to various mitogenic stimuli than did study participants in the placebo arm. No cannabis- or dronabinol-related changes were observed. Likewise, changes in cytokine (i.e., IFN γ , IL-2, TNF α) production among study participants in the cannabinoid study arms, and in NK activity among study participants in the dronabinol arm, were not significantly greater than among study participants receiving the placebo. No cannabis- or dronabinol-associated adverse effects were observed over the 21-day exposure period on the percentage of circulating CD4⁺ or CD8⁺ cells or on disease progression, as measured by viral load (Abrams

¹ Chapter 4 discusses Lutge et al. (2013), a systematic review that investigates the medical use of cannabis by patients with HIV/AIDS but does not specifically address the association between cannabis use and immune competence in this population.

et al., 2003). Overall, there were no “clear discernible negative changes” (p. 87S) among study participants who received dronabinol or cannabis as compared to those who received the placebo. Significant limitations of this study were the very short time period of cannabinoid exposure and the small number of study participants included in the study.

A longitudinal study evaluated the effects of recreational cannabis use on CD4⁺ and CD8⁺ T cell populations and disease progression in men infected with HIV (3,236 participants, of which 59 percent used cannabis) and men not infected with HIV (481 participants, of which 61 percent used cannabis) (Chao et al., 2008). HIV-negative and HIV-positive study participants were followed for a maximum of 18 and 11 years, respectively. After controlling for health risk behaviors and other potential confounders, any cannabis use and monthly or less frequent cannabis use were both associated with a statistically significant 1 percent decrease in CD4⁺ cell count among men not infected with HIV, while weekly or more frequent cannabis use was associated with a 5 percent decrease in CD8⁺ cell count among men infected with HIV. However, Chao et al. (2008, p. 5) state that there were no “clinically meaningful associations, adverse or otherwise, between use of marijuana . . . and T cell counts and percentages in either HIV-uninfected or HIV-infected men.” A major shortcoming of this study was the absence of information concerning the frequency and level of exposure to cannabis.

Thames et al. (2016) examined the independent and combined effects of HIV and cannabis smoking on neurocognitive function in 55 HIV positive and 34 HIV negative study participants who reported previously using cannabis for 12 months or more. As part of this study, the percentage of CD4⁺ T cells was monitored. Differences in the frequency of cannabis use were not associated with statistically significant differences in the nadir count of CD4⁺ T cells. A modest but statistically significant increase in the percentage of circulating CD4⁺ T cells ($p = 0.04$) and a statistically significant decrease in viral load ($p = 0.03$) were associated with light (i.e., 2–14 times per week) and moderate to heavy (i.e., 18–90 times per week) cannabis use as compared to nonusers. A shortcoming of this study was the small number of study participants.

Discussion of Findings

Collectively, the studies suggest that cannabis smoke and/or cannabinoids do not adversely affect the immune status of HIV patients. However, each of the four studies possessed major shortcomings in experimental design which could have contributed to the absence of adverse effects being observed in HIV patients who used cannabis or cannabinoids; these shortcomings include study durations that were insufficient to

observe adverse effects in the endpoints being measured, small numbers of study participants, and poorly defined and variable levels of cannabinoid exposure.

CONCLUSION 8-2 There is insufficient evidence to support or refute a statistical association between cannabis or dronabinol use and adverse effects on immune status in individuals with HIV.

Is There an Association Between Cannabis Use and the Immune Status of Individuals Infected with Viral Hepatitis C?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the immune status of individuals infected with HCV.

Primary Literature

HCV is a chronic disorder of the liver which can lead to fibrosis and progress to cirrhosis and ultimately to end-stage liver disease or hepatocellular carcinoma. Liver fibrosis is mediated, in part, through a chronic immune-mediated inflammatory response. A study of liver biopsies from 270 untreated patients with chronic hepatitis C was conducted in which patients were categorized as either nonusers, occasional cannabis users, or daily cannabis users (Hezode et al., 2005). A significantly higher proportion of daily cannabis users (68.5 percent)—as compared to occasional cannabis users (42.5 percent) or nonusers (39.7 percent)—had a fibrosis progression rate faster than the median fibrosis progression rate for the cohort as a whole. There was a statistically significant association between daily cannabis use and faster than median fibrosis progression rate when no cannabis use was the referent (OR, 3.4, 95% CI = 1.5–7.4). After controlling for potential confounders, including alcohol and tobacco use, daily cannabis use was also determined to be an independent predictor of severe fibrosis (OR, 2.3, 95% CI = 1.1–4.8). A subsequent prospective study investigated 690 patients infected with both HIV and HCV and who had no significant liver fibrosis or end-stage liver disease at baseline, of whom 40 percent smoked cannabis daily at study baseline (Brunet et al., 2013). This study found no statistically significant association between daily cannabis use and progression to significant liver fibrosis (hazard ratio, 1.02, 95% CI = 0.93–1.12). Finally, Liu et al. (2014) conducted a study to evaluate potential associations between cannabis use and liver disease progression

and outcomes from treatment for HCV. Among 376 participants for whom liver biopsies and cannabis use information was available, cannabis use as compared to nonuse was not significantly associated with fibrosis stage ($p = 0.66$) or with hepatic inflammation grade ($p = 0.75$). Among 348 participants, cannabis use as compared to nonuse was not significantly associated with steatosis as assessed by biopsies ($p = 0.32$). Compared to nonuse of cannabis, there was no statistically significant association between cannabis use and treatment outcomes as measured by rates of sustained viral response among 359 participants receiving interferon-based HCV antiviral treatment ($p = 0.13$).

Discussion of Findings

Although all three studies were of good quality, their results were mixed. Two studies suggested that cannabis use was not significantly associated with progression of liver disease or with fibrosis stage in HCV patients. Since chronic inflammation is a significant contributing factor to the progression of liver fibrosis, these findings appear to be consistent with the anti-inflammatory activity of cannabinoids observed in the immune competence literature reviewed above. However, a third study found that daily cannabis use was significantly associated with the severe fibrosis and faster progression of fibrosis, thereby complicating any conclusions about the association between liver disease progression and cannabis use. Overall, the available evidence that cannabis use is not associated with the progression of liver fibrosis and hepatic disease in individuals with HCV is stronger than the available evidence that cannabis use is associated with the progression of liver fibrosis and hepatic disease in individuals with HCV.

CONCLUSION 8-3 There is limited evidence of no statistical association between daily cannabis use and the progression of liver fibrosis or hepatic disease in individuals with viral hepatitis C (HCV).

Is There an Association Between Cannabis Use and Susceptibility to Oral Human Papilloma Virus (HPV)?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and susceptibility to oral HPV.

Primary Literature

Risk factors associated with oral HPV infection were investigated in a cross-sectional study involving 128 HIV-negative and 161 HIV-positive study participants (Muller et al., 2015). Cannabis use was identified as a statistically significant risk factor for detection of oral HPV in HIV-negative study participants (OR, 4.0, 95% CI = 1.3–12.4), although this risk was statistically nonsignificant after adjusting for other variables, including tobacco, alcohol, and other drug use (OR, 2.1, 95% CI = 0.6–7.5). By comparison, cannabis use was not a statistically significant risk factor for detection of oral HPV in HIV-positive individuals, whether before (OR, 1.6, 95% CI = 0.7–3.4) or after (OR, 1.3, 95% CI = 0.4–3.9) adjusting for potential confounders. The factors responsible for the differential effects between HIV-negative and HIV-positive individuals are unclear. Likewise, Kahn et al. (2015) conducted a cross-sectional study to evaluate the prevalence of oral HPV infection and to investigate associations between vaccination and oral infection in HIV-infected youth. The study included 272 HIV-infected study participants between the ages of 12 and 24 years, with a mean age of 21.5 years. In univariable analyses, no statistically significant association between lifetime cannabis use, as compared to non-use, and oral HPV infection was identified (OR, 0.68, 95% CI = 0.36–1.30). A significant limitation of both studies was the inability to determine whether regular cannabis use increased risky behavior that would predispose study participants to oral HPV infection. Likewise, there was no follow-up on whether cannabis altered the course of HPV infection or its downstream consequences.

Discussion of Findings

Kahn et al. (2015) reported no statistically significant association between cannabis use and oral HPV. Muller et al. (2015) reported that, prior to adjusting for potential confounders, cannabis use was significantly associated with oral HPV in HIV-negative individuals, but not in HIV-positive individuals. The plausibility of this finding is questionable in light of the fact that HIV-infected patients have decreased T cell-mediated immunity, which is critical in anti-viral immune responses, including against HPV. Therefore, it would be expected that HIV-infected patients would be at least as, if not significantly more, susceptible to HPV infection as would HIV-negative patients. A major limitation of Kahn et al. (2015) is that it is not possible to determine, based on the study design, whether the reported association between regular cannabis use and increased incidence of oral HPV in HIV-negative individuals is attributable to cannabis-mediated immune suppression or to other causes, such as increased high-risk behavior.

CONCLUSION 8-4 There is insufficient evidence to support or refute a statistical association between regular cannabis use and increased incidence of oral human papilloma virus (HPV).

Is There an Association Between Cannabis Use and *Aspergillus* Infection?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and infection with *Aspergillus*.

Primary Literature

Infection with *Aspergillus* species can be life-threatening in immunocompromised patients, including those with prolonged neutropenia, hematopoietic stem cell transplant, solid organ transplant, inherited or acquired immunodeficiencies, diabetes, corticosteroid use, or diabetes (Cescon et al., 2008; Denning et al., 1991). Cannabis has been demonstrated to harbor *Aspergillus* spores, and case reports suggest that cannabis use may be associated with aspergillosis in immunocompromised patients. For example, a letter published in the *Annals of Internal Medicine* in 1975 described a case of *Aspergillus fumigatus* pneumonitis in a 17-year-old male with chronic granulomatous disease. Heavy growth of *Aspergillus fumigatus* was observed in a culture taken from the patient's cannabis and pipe, and the author states that the "infection may have been acquired through inhalation of smoke from marijuana contaminated with fungi" (Chusid et al., 1975, p. 682). More recent case reports and case series have described aspergillosis in current or former cannabis users with acute myelogenous leukemia (Szyper-Kravitz et al., 2001), chronic myelogenous leukemia post bone marrow transplant (Hamadeh et al., 1988), small-cell lung cancer (Sutton et al., 1986), colorectal cancer (Cescon et al., 2008), renal transplant (Marks et al., 1996; Vethanayagam et al., 2000), chronic obstructive pulmonary disease (Sakkour et al., 2008), diabetes (Remington et al., 2015), and HIV/AIDS (Denning et al., 1991; Johnson et al., 1999). Aspergillosis has also been observed in current or former cannabis users with structural lung damage but who were not immunocompromised (Gargani et al., 2011) Many of the case reports involved smoking cannabis, although one involved a diabetic patient who inhaled vaporized cannabis for treatment of neuropathic pain (Remington et al., 2015). Box 8-1 describes a case series and a case-control study on the association between cannabis use and aspergillosis.

BOX 8-1 Cannabis and Aspergillosis

Denning et al. (1991) reported on 13 cases of pulmonary aspergillosis in patients with AIDS or asymptomatic HIV infection. Cannabis use was listed as a “possible underlying factor” in 4 of the 13 cases. However, the actual prevalence of cannabis use in this group may have been higher, since data on cannabis use was not available for seven patients (Denning et al., 1991, p. 656). Between November 1988 and March 1994, *Aspergillus* species were detected in induced sputum or bronchoalveolar lavage specimens collected from 19 HIV positive participants in the Pulmonary Complication of HIV Infection Study (Wallace et al., 1998). A nested case-control study of these 19 participants found that cannabis use at the time of entry into the study was not significantly associated with *Aspergillus* infection (Wallace et al., 1998). By contrast, neutropenia (i.e., neutrophil count <1,000 cells per cubic millimeter), a CD4 count <30 cells per cubic millimeter, corticosteroid use, and *Pneumocystis carinii* pneumonitis were among the factors that were significantly associated with *Aspergillus* infection.

Discussion of Findings

Sporadic case reports published over the last 40 years suggest that *Aspergillus* infection may be associated with cannabis use. The case-control study of *Aspergillus* infection in HIV positive patients did not find cannabis use to be significantly associated with the presence of the fungus in induced sputum or bronchoalveolar lavage specimens, although the number of study participants was small (Wallace et al., 1998). Despite the limited nature of the literature on aspergillosis and cannabis use, consensus guidelines and scientists suggest that immunocompromised patients avoid cannabis use due to its potential for increasing the risk of *Aspergillus* infection (Remington et al., 2015; Sullivan et al., 2001).

RESEARCH GAP

Research is needed to determine whether chronic cannabis smoke or cannabinoid treatment alters immune competence in healthy or immunocompromised individuals as evidenced by an increased incidence of infectious diseases; an extended duration of time to resolution of infectious diseases; and altered progression of cancer through the modulation of immune competence.

SUMMARY

One challenge associated with determining whether an agent alters immune competence is the diversity of the cellular elements that constitute the immune system and the many functions that these different cell types perform. The committee found a very limited number of studies in which the effects of cannabis use on the human immune system were assessed. Almost without exception, these evaluations were very narrow in scope, assessing only one or a few immunological endpoints and thus providing little information concerning the effects of cannabis use on immune status. Some studies were limited to determining the number of circulating leukocyte populations, such as T cells, with no assessments of cell function.

Although based on limited evidence, an interesting finding was the association between cannabis use in healthy individuals and a decrease in

BOX 8-2 Summary of Chapter Conclusions*

There is limited evidence of a statistical association between cannabis smoking and:

- A decrease in the production of several inflammatory cytokines in healthy individuals (8-1a)

There is limited evidence of no statistical association between cannabis use and:

- The progression of liver fibrosis or hepatic disease in individuals with viral hepatitis C (HCV) (daily cannabis use) (8-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- Other adverse immune cell responses in healthy individuals (cannabis smoking) (8-1b)
- Adverse effects on immune status in individuals with human immunodeficiency virus (HIV) (cannabis or dronabinol use) (8-2)
- Increased incidence of oral human papilloma virus (HPV) (regular cannabis use) (8-4)

* Numbers in parentheses correspond to chapter conclusion numbers.

the production of certain inflammatory cytokines. Similar findings have been reported in animal- and cell-based experiments. More studies will need to be conducted to verify the anti-inflammatory activity of cannabis in humans. Presently, there is either insufficient or no data to ascertain whether cannabis use alters other immune responses in healthy individuals. In addition, several studies have evaluated the effects of cannabis on either susceptibility to, or progression of, infectious diseases—namely, HIV, HCV, or the papilloma virus. There is insufficient evidence to determine whether there is an association between regular use of cannabis and increased incidence of papilloma virus or between cannabis or cannabinoid (e.g., dronabinol) use and adverse effects on immune status among individuals with HIV. In addition, there is limited evidence to support the conclusion that cannabis use does not enhance the progression of liver disease in HCV patients. Box 8-2 provides a summary of the findings from this chapter.

It is important to emphasize that many of the studies in which the effects of cannabis on the immune system were evaluated possess significant shortcomings in experimental design, such as small numbers of study participants, a study that was insufficient to determine adverse effects, a narrow scope of immunological assessments, and limited information concerning the levels of cannabis exposure. Each of these limitations precludes drawing conclusions concerning the effects of cannabis on immune competence in humans with any reasonable level of certainty.

REFERENCES

- Abo-Elnazar, S., M. Moaaz, H. Ghoneim, T. Molokhia, and W. El-Korany. 2014. Th17/Treg imbalance in opioids and cannabinoids addiction: Relationship to NF- κ B activation in CD4+ T cells. *Egyptian Journal of Immunology* 21(2):33–47.
- Abrams, D. I., J. F. Hilton, R. J. Leiser, S. B. Shade, T. A. Elbeik, F. T. Aweeka, N. L. Benowitz, B. M. Brecht, B. Kosel, J. A. Aberg, S. G. Deeks, T. F. Mitchell, K. Mulligan, P. Bacchetti, J. M. McCune, and M. Schambelan. 2003. Short-term effects of cannabinoids in patients with HIV-1 infection: A randomized, placebo-controlled clinical trial. *Annals of Internal Medicine* 139(4):258–266.
- Brecht, B. M., D. Higuera-Alhino, S. B. Shade, S. J. Hebert, J. M. McCune, and D. I. Abrams. 2002. Short-term effects of cannabinoids on immune phenotype and function in HIV-1-infected patients. *Journal of Clinical Pharmacology* 42(11 Suppl):82S–89S.
- Brunet, L., E. E. M. Moodie, K. Rollet, C. Cooper, S. Walmsley, M. Potter, and M. B. Klein. 2013. Marijuana smoking does not accelerate progression of liver disease in HIV-hepatitis C coinfection: A longitudinal cohort analysis. *Clinical Infectious Diseases* 57(5):663–670.
- Cescon, D. W., A. V. Page, S. Richardson, M. J. Moore, S. Boerner, and W. L. Gold. 2008. Invasive pulmonary aspergillosis associated with marijuana use in a man with colorectal cancer. *Journal of Clinical Oncology* 26(13):2214–2215.

- Chao, C., L. P. Jacobson, D. Tashkin, O. Martinez-Maza, M. D. Roth, J. B. Margolick, J. S. Chmiel, C. Rinaldo, Z. F. Zhang, and R. Detels. 2008. Recreational drug use and T lymphocyte subpopulations in HIV-uninfected and HIV-infected men. *Drug and Alcohol Dependence* 94(1–3):165–171.
- Chusid, M. J., J. A. Gelfand, C. Nutter, and A. S. Fauci. 1975. Letter: Pulmonary aspergillosis, inhalation of contaminated marijuana smoke, chronic granulomatous disease. *Annals of Internal Medicine* 82(5):682–683.
- Denning, D. W., S. E. Follansbee, M. Scolaro, S. Norris, H. Edelstein, and D. A. Stevens. 1991. Pulmonary aspergillosis in the acquired immunodeficiency syndrome. *New England Journal of Medicine* 324(10):654–662.
- Gargani, Y., P. Bishop, and D. W. Denning. 2011. Too many mouldy joints—marijuana and chronic pulmonary aspergillosis. *Mediterranean Journal of Hematology and Infectious Diseases* 3(1):e2011005.
- Gill, A. J., and D. L. Kolson. 2014. Chronic inflammation and the role for cofactors (hepatitis C, drug abuse, antiretroviral drug toxicity, aging) in HAND persistence. *Current HIV/AIDS Reports* 11(3):325–335.
- Hamadeh, R., A. Ardehali, R. M. Locksley, and M. K. York. 1988. Fatal aspergillosis associated with smoking contaminated marijuana, in a marrow transplant recipient. *Chest* 94(2):432–433.
- Hezode, C., F. Roudot-Thoraval, S. Nguyen, P. Grenard, B. Julien, E. S. Zafrani, J. M. Pawlostky, D. Dhumeaux, S. Lotersztajn, and A. Mallat. 2005. Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. *Hepatology* 42(1):63–71.
- Jatoi, A., J. I. Yamashita, J. A. Sloan, P. J. Novotny, H. E. Windschitl, and C. L. Loprinzi. 2002. Does megestrol acetate down-regulate interleukin-6 in patients with cancer-associated anorexia and weight loss? A north central cancer treatment group investigation. *Supportive Care in Cancer* 10(1):71–75.
- Johnson, T. E., R. R. Casiano, J. W. Kronish, D. T. Tse, M. Meldrum, and W. Chang. 1999. Sino-orbital aspergillosis in acquired immunodeficiency syndrome. *Archives of Ophthalmology* 117(1):57–64.
- Kahn, J. A., B. J. Rudy, J. Xu, E. A. Secord, B. G. Kapogiannis, S. Thornton, and M. L. Gillison. 2015. Behavioral, immunologic, and virologic correlates of oral human papillomavirus infection in HIV-infected youth. *Sexually Transmitted Diseases* 42(5):246–252.
- Keen, L., II, and A. D. Turner. 2015. Differential effects of self-reported lifetime marijuana use on interleukin-1 alpha and tumor necrosis factor in African American adults. *Journal of Behavioral Medicine* 38(3):527–534.
- Klein, T. W. 2005. Cannabinoid-based drugs as anti-inflammatory therapeutics. *Nature Reviews Immunology* 5(5):400–411.
- Liu, T., G. T. Howell, L. Turner, K. Corace, G. Garber, and C. Cooper. 2014. Marijuana use in hepatitis C infection does not affect liver biopsy histology or treatment outcomes. *Canadian Journal of Gastroenterology & Hepatology* 28(7):381–384.
- Lutge, E. E., A. Gray, and N. Siegfried. 2013. The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. *Cochrane Database of Systematic Reviews* (4):CD005175.
- Marks, W. H., L. Florence, J. Lieberman, P. Chapman, D. Howard, P. Roberts, and D. Perkinson. 1996. Successfully treated invasive pulmonary aspergillosis associated with smoking marijuana in a renal transplant recipient. *Transplantation* 61(12):1771–1774.
- Meier, M. H., A. Caspi, M. Cerda, R. J. Hancox, H. Harrington, R. Houts, R. Poulton, S. Ramrakha, W. M. Thomson, and T. E. Moffitt. 2016. Associations between cannabis use and physical health problems in early midlife: A longitudinal comparison of persistent cannabis versus tobacco users. *JAMA Psychiatry* 73(7):731–740.

- Muller, K., J. Kazimiroff, M. Fatahzadeh, R. V. Smith, M. Wiltz, J. Polanco, R. M. Grossberg, T. J. Belbin, H. D. Strickler, R. D. Burk, and N. F. Schlecht. 2015. Oral human papillomavirus infection and oral lesions in HIV-positive and HIV-negative dental patients. *Journal of Infectious Diseases* 212(5):760–768.
- Pacifici, R., P. Zuccaro, M. Farre, S. Poudevida, S. Abanades, S. Pichini, K. Langohr, J. Segura, and R. De La Torre. 2007. Combined immunomodulating properties of 3,4-methylenedioxy-methamphetamine (MDMA) and cannabis in humans. *Addiction* 102(6):931–936.
- Remington, T. L., J. Fuller, and I. Chiu. 2015. Chronic necrotizing pulmonary aspergillosis in a patient with diabetes and marijuana use. *Canadian Medical Association Journal* 187(17):1305–1308.
- Sakkour, A., T. Wang, and D. Tashkin. 2008. A 56-year-old woman with COPD and multiple pulmonary nodules. *Chest* 133(2):566–569.
- Sullivan, K. M., C. A. Dykewicz, D. L. Longworth, M. Boeckh, L. R. Baden, R. H. Rubin, and K. A. Sepkowitz. 2001. Preventing opportunistic infections after hematopoietic stem cell transplantation: The Centers for Disease Control and Prevention, Infectious Diseases Society of America, and American Society for Blood and Marrow Transplantation practice guidelines and beyond. *Hematology* 2001(1):392–421.
- Sutton, S., B. L. Lum, and F. M. Torti. 1986. Possible risk of invasive pulmonary aspergillosis with marijuana use during chemotherapy for small cell lung cancer. *Drug Intelligence & Clinical Pharmacy* 20(4):289–291.
- Szyper-Kravitz, M., R. Lang, Y. Manor, and M. Lahav. 2001. Early invasive pulmonary aspergillosis in a leukemia patient linked to aspergillus contaminated marijuana smoking. *Leukemia & Lymphoma* 42(6):1433–1437.
- Thames, A. D., Z. Mahmood, A. C. Burggren, A. Karimian, and T. P. Kuhn. 2016. Combined effects of HIV and marijuana use on neurocognitive functioning and immune status. *AIDS Care: Psychological and Socio-Medical Aspects of AIDS/HIV* 28(5):628–632.
- Vethanayagam, D., S. Pugsley, E. J. Dunn, D. Russell, J. M. Kay, and C. Allen. 2000. Exogenous lipid pneumonia related to smoking weed oil following cadaveric renal transplantation. *Canadian Respiratory Journal* 7(4):338–342.
- Wallace, J. M., R. Lim, B. L. Browdy, P. C. Hopewell, J. Glassroth, M. J. Rosen, L. B. Reichman, and P. A. Kvale. 1998. Risk factors and outcomes associated with identification of *Aspergillus* in respiratory specimens from persons with HIV disease. Pulmonary complications of HIV infection study group. *Chest* 114(1):131–137.

9

Injury and Death

Chapter Highlights

- Cannabis use prior to driving increases the risk of being involved in a motor vehicle accident.
- In states where cannabis use is legal, there is increased risk of unintentional cannabis overdose injuries among children.
- It is unclear whether and how cannabis use is associated with all-cause mortality or with occupational injury.

This chapter discusses the association between cannabis use and all-cause mortality, occupational injury, motor vehicle accidents, and overdose injuries and death. These health endpoints are distinguished not only by their status as significant public health issues but also by the extent to which directed public health actions and policy changes hold the potential for lessening their detrimental impacts on population health. Motor vehicle accidents are a leading cause of death and injury in the United States, and occupational injuries, especially those that permanently limit an individual's capacity to perform tasks at home and in the workplace, impose substantial economic burdens on workers, employers, and communities. If research indicates that cannabis use is positively associated with either occupational injury or motor vehicle accidents, evidence-based policies limiting the use of cannabis while driving or in the workplace could potentially reduce the incidence of cannabis-related

accidents and injury. Similarly, research suggesting that cannabis use is linked to mortality could prompt the development of programs to educate health professionals and the general public on the effects of cannabis use and positively influence cannabis-related mortality rates.

In this chapter, the committee reviews and draws conclusions from the findings of six good- to fair-quality systematic reviews and 18 primary literature articles that best address the committee's research questions of interest. Study limitations and research gaps are noted, and the strength of the available evidence is weighed in five formal conclusions.

ALL-CAUSE MORTALITY

The Institute of Medicine (IOM) report *Marijuana and Medicine: Assessing the Science Base* states that “epidemiological data indicate that in the general population marijuana use is not associated with increased mortality” (IOM, 1999, p. 109). More recently, modeling studies have estimated that a substantial disease burden—and the associated decrements in the quality and length of life—can be attributed to cannabis use (Degenhardt et al., 2013; Imtiaz et al., 2016). By contrast, a recent systematic review informed by epidemiological data did not report a statistically significant association between cannabis use and mortality (Calabria et al., 2010). This section reviews the available literature to assess the evidence and develop conclusions about cannabis-related mortality.

Is There an Association Between Cannabis Use and All-Cause Mortality?

Systematic Reviews

Calabria et al. (2010) conducted a systematic review to determine the association between cannabis use and all-cause mortality in the general population, and they identified two prospective epidemiological cohort studies relevant to this health endpoint.¹ A meta-analysis of these studies was not performed; consequently, the results of the individual studies are presented below.

Sidney et al. (1997) assessed the risk of mortality associated with cannabis use in a cohort of 65,171 individuals ages 15 to 49 years who were enrolled in the Kaiser Permanente Medical Care Program and followed

¹ The review also addressed the association between cannabis use and health endpoints that are often or always fatal, such as motor vehicle accidents, cancer, and suicide. These health endpoints are not reviewed in this section, as they are discussed elsewhere in the report.

for a mean length of 10 years. Compared to men who never smoked or who smoked experimentally (i.e., cannabis use on one to six occasions), those who were current smokers were at a significantly increased risk of all-cause mortality after adjusting for several potential confounders, including cigarette smoking, alcohol use, and demographic and socioeconomic factors (relative risk [RR], 1.33, 95% confidence interval [CI] = 1.11–1.59). Notably, among men who currently smoked cannabis, the relative risk of mortality due to AIDS was significantly elevated (RR, 1.90, 95% CI = 1.33–2.73), while the risk of mortality due to known causes other than AIDS was not significantly elevated (RR, 1.12, 95% CI = 0.89–1.39). After accounting for potential confounders, women who currently smoked cannabis were not at a significantly increased risk of all-cause mortality compared to those who had never smoked or who had smoked experimentally (RR, 1.09, 95% CI = 0.80–1.48). Among men who currently smoked cannabis, the frequency of use had only a small effect on the risk of all-cause mortality: those who smoked at least once per week and those who smoked daily were at, respectively, 46 percent (RR, 1.46, 95% CI = 1.19–1.79) and 43 percent (RR, 1.43, 95% CI = 1.08–1.90) greater relative risk of all-cause mortality than nonusers and experimental users. In women, the frequency of use among current smokers had a larger impact on the risk of mortality: those who smoked at least once a week had a less elevated risk of mortality than those who smoked daily as compared to nonusers and experimental users (RR, 1.23, 95% CI = 0.84–1.80 versus RR, 1.44, 95% CI = 0.80–2.56).

Andreasson and Allebeck (1990) reported that among 45,540 Swedish male military conscripts followed for 15 years, the relative risk of mortality was elevated for those who reported having smoked cannabis more than 50 times by the time of conscription compared to nonsmokers (RR, 2.8, 95% CI = 1.9–4.1). After adjusting for multiple confounders, including smoking tobacco, alcohol use, and other drug use, the relative risk of mortality for heavy cannabis smokers was no longer significantly elevated compared with nonsmokers (RR, 1.2, 95% CI = 0.7–1.9). Similarly, participants who reported having smoked cannabis on fewer than 50 occasions by the time of conscription were not at significantly greater risk than nonsmokers after adjustments (RR, 0.7, 95% CI = 0.4–1.2).

Primary Literature

Muhuri and Gfroerer (2011) assessed the risk of all-cause mortality associated with the use of cannabis and other illegal drugs among 20,983 adults over a 15-year follow-up period. After adjusting for confounders, including alcohol use, cigarette smoking, and demographic factors, individuals who reported using cannabis, but not other substances (i.e.,

cocaine, heroin, hallucinogens, inhalants), at baseline were not at increased risk of all-cause mortality compared with individuals who reported not using cannabis or other substances at baseline (hazard ratio [HR], 1.07, 95% CI = 0.85–1.33). Manrique-Garcia et al. (2016) conducted a follow-up study of a cohort of 50,373 Swedish male military conscripts to characterize the potential association between mortality and heavy cannabis use (i.e., using cannabis more than 50 times by 18 years of age). Among the cohort as a whole, heavy cannabis use was associated with a significantly increased risk of mortality compared with nonuse (HR, 1.4, 95% CI = 1.1–1.8). Notably, heavy cannabis use as compared with nonuse did not appreciably affect the risk of mortality among individuals with psychotic disorders—for whom the risk of mortality was particularly elevated (HR, 3.8, 95% CI = 2.6–6.2 versus HR, 3.7, 95% CI = 3.1–4.4).

Discussion of Findings

Sidney et al. (1997) found a statistically significant association between cannabis use and increased risk of all-cause mortality among men diagnosed with AIDS, but not among men without this diagnosis or among women. The authors suggest that the relationship between cannabis use and all-cause mortality among male AIDS patients was not causal; instead, it “most likely represented uncontrolled confounding by male homosexual behavior” (Sidney et al., 1997, p. 589). Limitations in Sidney et al. (1997) include the use of self-report without biological validation to assess patterns of cannabis use; the lack of post-baseline assessments of cannabis use, by which changes over time in the frequency of use could be documented; a lack of data on other substance use, creating the possibility for residual confounding; and, the inability to follow participants into later age, where potential long-term health effects of cannabis use may have emerged.

After accounting for potential confounders, Andreasson and Allebeck (1990) found no statistically significant association between cannabis use and mortality. Furthermore, although a high proportion of deaths among participants who reported smoking cannabis on 50 or more occasions by the time of conscription were due to suicide or uncertain suicide, use of narcotics was also common in these incidents, leading the authors to suggest that a “significant share of the mortality associated with cannabis abuse in this study is attributable to intravenous drug abuse” (Andreasson and Allebeck, 1990, p. 14). Limitations of the study include the use of non-anonymous self-report to collect data on patterns of cannabis use, and the lack of any post-baseline assessments of cannabis use.

Findings from Muhuri and Gfroerer (2011) are based on data from the 1991 National Health Interview Survey’s Drug and Alcohol Use supple-

mental questionnaire, and they indicate a lower prevalence of cannabis use than that seen in the 1991 National Household Survey on Drug Abuse (NHSDA) (45.2 percent versus 52.7 percent). If this discrepancy in the prevalence of cannabis use reported by two national surveys conducted in the same year is the result of underreporting by participants who died during the follow-up period, the mortality risk associated with cannabis use could have been underestimated. Other limitations include the use of self-report to collect data on patterns of cannabis use and the lack of post-baseline assessments to detect changes in cannabis use. Strengths of the study include a base population from a national household sample and an analysis that excluded users of other important illicit drug categories—heroin, cocaine, hallucinogens, and inhalants.

Findings from Manrique-Garcia et al. (2016) have several limitations. Risk estimates are based on cannabis use as of the time of prescription rather than lifetime cannabis exposure and therefore do not account for cannabis use during the ~40 year follow-up period. Similarly, data on potential confounders after the time of prescription is unavailable, so the extent to which they affected study participants and potentially impacted all-cause mortality risk is unknown. Finally, since data on cannabis use was collected by non-anonymous self-report without biological validation, cannabis use may have been underreported.

There is an overall dearth of cohort studies empirically assessing general population cannabis use and all-cause mortality. Although the available evidence suggests that cannabis use is not associated with an increased risk of all-cause mortality, the limited nature of that evidence makes it impossible to have confidence in these findings. These conclusions are not informed by the results of existing large-scale modeling studies that synthesized data from a variety of sources to estimate the burden of disease attributable to cannabis use (Degenhardt et al., 2013; Imtiaz et al., 2016). Although these studies were methodologically rigorous, their direct applicability to actual cannabis-related mortality rates in the United States is uncertain. Consequently, the committee chose not to include them in this review. Also excluded from review were studies of mortality among persons with known cannabis addiction or dependence, those who have been under medical treatment for these disorders, or those who were identified through a country's criminal justice system, due to presence in these populations of important and often inadequately controlled confounders such as concurrent mental illness and poly-substance abuse.

CONCLUSION 9-1 There is insufficient evidence to support or refute a statistical association between self-reported cannabis use and all-cause mortality.

OCCUPATIONAL INJURY

The Bureau of Labor Statistics reported that 4,821 fatal occupational injuries occurred in the United States in 2014, or about 3.4 fatal injuries for every 100,000 full-time equivalent workers (BLS, 2016). Private industry and state and local government employers reported another 3,486,400 nonfatal occupational injuries in the same year (BLS, 2015). The economic impact of these injuries is considerable. Leigh (2011) estimated that the average medical costs per nonfatal and fatal injury in 2007 were \$5,369 and \$55,595, respectively. Nationally, the medical and indirect costs of occupational injuries (fatal and nonfatal) totaled \$191.83 billion in 2007 (Leigh, 2011). Marucci-Wellman et al. (2015) estimated that in the United States the direct workers' compensation cost of the most severe, nonfatal occupational injuries was over \$51 billion in 2010.²

Concurrent with this economic and public health burden is the increasing prevalence of cannabis use among employed U.S. adults ages 18 and older (Azofeifa et al., 2016). In 2015, 14.4 percent of U.S. adults ages 18 and older with full-time employment reported using cannabis during the previous year (CBHSQ, 2016, pp. 246–247). Among those employed part-time, the proportion was higher, at 17.8 percent (CBHSQ, 2016, pp. 246–247).³

Determining whether an association exists between cannabis use and occupational injury is the subject of ongoing research. According to the 1994 National Research Council and IOM report *Under the Influence?: Drugs and the American Workforce*, evidence on the relationship between employee drug use and accidents in the workplace is mixed (NRC and IOM, 1994, p. 144). This section updates these findings with a review of the current evidence on cannabis use and occupational injury.

Is There an Association Between Cannabis Use and Occupational Injury?

Systematic Review

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and occupational injury.

² Cost estimate is in 2010 dollars.

³ These percentages correspond to 17,042,000 and 5,770,000 U.S. adults ages 18 or older with full-time and part-time employment, respectively.

Primary Literature

The committee identified six primary literature articles addressing the association between cannabis use and occupational injury. Case series of occupational fatalities, with or without forensic investigation, were not considered if there was no consideration of risk compared to non-cannabis-exposed groups.

To investigate the potential association between cannabis use and work-related and non-work-related injuries and accidents, Wadsworth et al. (2006) sent questionnaires on drug use, history of accidents and injuries, and problems with memory or attention to 30,000 residents of two communities in Wales. Based on data from 7,979 completed questionnaires, there was no statistically significant association between cannabis use in the previous year and the risk of minor occupational injuries (i.e., work-related injuries not requiring medical attention) (odds ratio [OR], 1.17, 95% CI = 0.74–1.86), work-related accidents at work requiring medical attention (OR, 0.91, 95% CI = 0.43–1.89), or work-related traffic accidents (OR, 3.01, 95% CI = 0.89–10.17) as compared to no illicit drug use and after adjusting for potentially confounding risk factors (e.g., mental and physical health problems, history of risk-taking behavior, limited work experience).

Wadsworth et al. (2006) also stratified the study population into groups with low and high levels of potential risk factors for work-related accidents and injuries, and they determined the association between cannabis use and the risk for occupational injury for each. Compared to participants who did not use illicit drugs in the previous year and who had few other risk factors, those who used cannabis in the previous year had a significantly elevated risk of suffering minor occupational injuries in the past year if they also had several other risk factors (OR, 8.49, 95% CI = 5.37–13.42), but not if they had few other risk factors (OR, 1.10, 95% CI = 0.47–2.57). The risk of suffering a work-related accident requiring medical attention in the previous year was also significantly elevated for participants who used cannabis in the previous year and had several other risk factors (OR, 3.85, 95% CI = 1.89–7.82), but not for participants who used cannabis in the previous year and had few other risk factors (OR, 0.92, 95% CI = 0.22–3.92) when compared to those who reported no illicit drug use in the previous year and who had few other risk factors. When individuals who used no illicit drugs in the previous year and who had few other risk factors were the referent, the risk of work-related traffic accidents in the previous year was significantly increased for individuals who used cannabis in the previous year, whether or not they had high levels (OR, 6.06, 95% CI = 1.37–26.77) or low levels (OR, 3.24, 95% CI = 1.19–8.79) of other risk factors.

Hoffmann and Larison (1999) used data on 9,097 full- and part-time employees ages 18 and older who participated in the 1994 NHSDA to

evaluate the potential association between cannabis use and the risk of work-related accidents (i.e., accidents that occur at work and that result in damage to property or equipment, injury to oneself, and/or injury to others). They found no statistically significant association between any category of former cannabis use (i.e., used 3 or more years ago, used 1–3 years ago) or any category of current use (i.e., used 1–2 days in past year, used 3–51 days in the past year, used at least weekly in past year) and the risk of work-related accidents as compared to never using cannabis.⁴

Shipp et al. (2005) conducted a cross-sectional study to assess the association between self-reported nonfatal occupational injuries and the self-reported use of substances among 3,265 students attending high school in Texas who indicated that they currently (or had previously) worked for pay. Compared to currently employed students who did not smoke cannabis, those who reported using cannabis on one to nine occasions in the previous 30 days reported a significantly increased risk of occupational injury (OR, 1.37, 95% CI = 1.06–1.77) after adjusting for potential confounders, including year in high school, biological sex, and ethnicity. Heavier cannabis use was associated with higher risk: students who reported using cannabis more than 40 times in the past 30 days were more than twice as likely to have suffered a nonfatal occupational injury as those who did not use cannabis (OR, 2.47, 95% CI = 1.64–3.71) during this period. Adjusting for intensity of work (hours of work per week) decreased the strength of the association between cannabis use and occupational injury; nevertheless, that association remained statistically significant for students who had used cannabis one or more times over the course of their lifetimes (1 to 9 times: OR, 1.45, 95% CI = 1.10–1.90; 10 to 39 times: OR, 1.46, 95% CI = 1.01–2.12; 40+ times: OR, 1.87, 95% CI = 1.38–5.34) or 40 or more times in the previous 30 days (OR, 2.23, 95% CI = 1.34–3.71) as compared to students who did not use cannabis during these periods.

To investigate the association between cannabis use and occupational injury, urine samples collected from individuals working in the United States who had experienced an occupational injury were tested for the presence of cannabis metabolites and were compared to samples collected from individuals selected for a random employee drug test (Price, 2014). To control for the potential confounding effect of other substances, individuals with samples containing amphetamines, phencyclidine, or cocaine or opiate metabolites were removed from the analysis. Among the

⁴ ORs for these variables ranged from 1.51 for “used 1–2 days in past year” to 0.98 for “used 3–51 days in past year,” where the referent was never use of cannabis. Hoffmann and Larison (1999) did not provide confidence intervals for these ORs, though they indicated in the text that none achieved statistical significance at the $p < 0.05$ level.

remaining 961 cases and 2,834 controls, individuals whose urine samples contained detectable levels of cannabis metabolites were not significantly more likely to have suffered an occupational injury than those whose samples did not (OR, 0.814, 95% CI = 0.625–1.060).

Macdonald et al. (2010) conducted a literature review to answer several research questions related to workplace drug testing for cannabis, including whether employees who report using cannabis or who test positive for cannabis are at an increased risk for occupational injuries. Findings from the reviewed studies were mixed, with not all studies showing a statistically significant association between cannabis use and occupational injury. The authors also sought to determine whether chronic cannabis users have cognitive deficits that place them at an increased risk for occupational injuries, and they reported that although some studies suggest an association between cannabis use and reduced cognitive functioning, the impact of any such deficits on the risk of occupational injury has not been determined.

Dong et al. (2015) evaluated longitudinal data on 12,686 participants in the National Longitudinal Survey of Youth in order to identify factors associated with work-related incidents resulting in injury or illness. Among participants ages 14 to 22 years at study baseline and who reported working in construction between 1988 and 2000, there was no statistically significant association between either lifetime cannabis use on 1–10 occasions (OR, 1.04, 95% CI = 0.94–1.15) or lifetime cannabis use on 11 or more occasions (OR, 1.10, 95% CI = 0.99–1.21) and the incidence of occupational injury or illness when never use of cannabis was the referent.

In addition to the articles reviewed above, the committee identified several articles that—while relevant—were published prior to 1999 (Kaestner and Grossman, 1995, 1998; Zwerling et al., 1990) or that considered research questions closely related—but not identical—to the one addressed here (Fransen et al., 2006). Although these articles did not directly inform the committee's conclusions, they aided the committee in orienting themselves to the broader literature on risk factors for occupational injury.

Discussion of Findings

Although Wadsworth et al. (2006, p. 11) concluded that their findings “suggest a detrimental impact of cannabis use on safety that is apparent both in and out of the workplace,” they also list several limitations of the study and recommend caution in interpreting its results. Data on cannabis use was derived from self-report and did not measure duration or frequency of cannabis use nor the timing of cannabis use in relation to accidents or injuries. Furthermore, the study may not have completely

controlled for the effect of potential confounders, which may work independently of, or interactively with, cannabis use to modify the risk of occupational injuries or accidents. Finally, the risk for occupational injury posed by cannabis use may be attenuated by processes of self-selection in which cannabis users choose on average to work in lower-risk occupations and nonusers choose to work in higher-risk occupations.

Findings from Hoffmann and Larison (1999) also have several limitations. First, the study did not distinguish between work-related accidents resulting in damage to property and those resulting in injury. Second, the study did not determine whether cannabis use took place while at work; consequently, this type of cannabis use could pose a risk for occupational injury, even if current or former cannabis use in general does not. Third, it is not possible to determine from the NHSDA data whether cannabis use occurred proximate to the injury or whether it preceded or followed an occupational accident.

Shipp et al. (2005) note that the scarcity of research on the association between substance abuse and occupational injuries in adolescent populations prevents the comparison of their results with those from other studies. Because the students who were absent from school on the day of the survey may have had a higher or lower risk of injury compared to students who completed the survey, the potential for selection bias exists. Other limitations of the study include the inability to determine whether cannabis use occurred during work hours or at another time, whether cannabis use preceded or followed the injury, or how closely in time the two events occurred.

In Price (2014), urine samples were collected from men and women of different ages living in different states and employed in a variety of industries with unequal levels of safety sensitivity. The analysis did not control for these variables or determine whether they affect the risk of occupational injury. Furthermore, the study results could not be used to distinguish between recent and remote cannabis use or to determine the chronicity of cannabis use or the extent of an individual's tolerance for cannabis.

Results from Dong et al. (2015) were limited to those participants who reported working in construction and do not address the potential association between cannabis use and the risk of occupational injury in other industries. Participants who stated they had experienced an occupational injury during a specific time period were not asked how many such injuries occurred. As a result, the study may have underestimated the true number and risk of occupational injuries. Finally, the reference period for survey questions were long and changed over the course of the study, creating the possibility for recall bias.

In addition to these limitations, the studies were extremely diverse

in terms of the characteristics of study participants and their occupations, the specificity and scope of data on cannabis use and occupational injuries, and the extent to which the authors effectively controlled or accounted for potential confounders or effect modifiers. In light of the diversity among and limitations of these studies, it was not possible to determine whether general, nonmedical cannabis use is associated with a clearly increased risk of occupational accidents and injuries across a broad range of occupational and industrial settings in the absence of other important risk factors.

CONCLUSION 9-2 There is insufficient evidence to support or refute a statistical association between general, nonmedical cannabis use and occupational accidents or injuries.

MOTOR VEHICLE CRASHES

In 2011, motor vehicle crashes (MVCs) were the leading cause of death among U.S. adolescents and adults ages 16 to 25 years (NHTSA, 2015). Among all age groups, MVCs occurring in 2014 resulted in more than 32,000 fatalities and more than 2 million nonfatal injuries in the United States (CDC, 2016a; NHTSA, 2016).⁵ Nationally, the combined medical and work loss costs associated with these fatal and nonfatal injuries is substantial at \$44 and \$51.3 billion, respectively (Bergen et al., 2014; CDC, 2015).⁶

In 2014, 3.2 percent of individuals ages 16 to 25 years reported driving while intoxicated by cannabis (Azofeifa et al., 2015), and the prevalence of THC metabolites detected in the blood or oral fluids of weekend nighttime drivers participating in the National Roadside Survey rose from 8.6 percent in 2007 to 12.6 percent in 2013–2014 (Berning et al., 2015). Given the public health burden of MVC-related morbidity and mortality and the

⁵ NHTSA defines a fatal crash as “a police-reported crash involving a motor vehicle in transport on a trafficway in which at least one person dies within 30 days of the crash.” Total includes drivers and passengers of motor vehicles, motorcyclists, pedestrians, and cyclists (NHTSA, 2016). Data on nonfatal injuries obtained from the Centers for Disease Control and Prevention’s (CDC’s) Web-based Injury Statistics Query and Reporting System (WISQARS). Total includes all unintentional injuries that occurred on a public road or highway and were traffic related and that resulted in an emergency department visit (CDC, 2016a).

⁶ Total lifetime medical and work loss costs associated with fatal injuries consequent to MVC, based on MVCs occurring in 2013, was \$44 billion (CDC, 2015). Total lifetime medical (\$18.4 billion) and work loss (\$32.9 billion) costs associated with nonfatal injuries consequent to MVC, based on MVCs occurring in 2012, was \$51 billion (Bergen et al., 2014). Work loss costs are defined as “estimates of how much a person who died in a motor vehicle crash would have earned over the course of their life, had they not died,” and include salary, estimated benefits, and value of household work (CDC, 2015).

presence of cannabis use and intoxication while driving, there is a need for research to understand the effects of cannabis use on the incidence and severity of motor vehicle crashes and the safety and performance of drivers.

Is There an Association Between Cannabis Use and Motor Vehicle Crashes?

Systematic Reviews

The committee identified a total of six systematic reviews of fair or good quality that summarized the association between driving under the influence of cannabis (DUIC) and MVCs (Asbridge et al., 2012; Calabria et al., 2010; Elvik, 2013; Hartman and Huestis, 2013; Li et al., 2012; Rogeberg and Elvik, 2016). Rogeberg and Elvik (2016) was both the most comprehensive and most recently published systematic review. This review pooled studies reviewed in three earlier meta-analyses (Asbridge et al., 2012; Elvik, 2013; Li et al., 2012) and also performed a structured search of online databases. Calabria et al. (2010) evaluated the association between DUIC and fatal MVCs only, but, with the exception of Bedard et al. (2007), all of the studies in this earlier review were also included in Rogeberg and Elvik (2016). Bedard et al. (2007) was excluded by Rogeberg and Elvik (2016) because it was an analysis of cross-sectional data collected by the U.S. Fatal Accident Reporting System registry.

The meta-analysis by Rogeberg and Elvik (2016) summarized evidence from 21 case-control or culpability studies in 13 countries with a combined sample count of 239,739 participants. There were a total of 28 estimates available from these 21 observational studies. The authors of this systematic review limited their analysis to evidence from either case-control studies or culpability studies and did not include evidence from cross-sectional or cohort studies. The primary criterion for inclusion in the review was the quality of information that indicated cannabis use (i.e., laboratory analyses of blood samples, saliva samples, and urine samples; prescriptions; or self-report) and whether cannabis had been used while driving or enough time prior to driving for effects to still persist. The authors included a wide range of recent studies, including non-peer-reviewed data published by Compton and Berning (2015). Rogeberg and Elvik (2016) argued that culpability studies need to be adjusted for baseline culpability rates because the odds of culpable MVCs associated with DUIC are de facto higher than the overall increase in crash risk. Another important strength of this review is the careful adjustment for potential confounders, including alcohol, in the analysis.

Overall, the meta-analysis by Rogeberg and Elvik (2016) found that

DUIC, as indicated by self-reported cannabis use or the presence of THC metabolite in blood, saliva, or urine, was associated with 20 to 30 percent higher odds of an MVC. The authors described the magnitude of this association as low to moderate in range, and the committee agrees with that assessment. Specifically, the estimated ORs were 1.36 (95% CI = 1.15–1.61) for an analysis that used a random-effects approach and 1.22 (95% CI = 1.10–1.36) for a meta-regression analysis using a precision effect estimate with standard errors (PEESE) technique. Subgroup analyses that accounted for alcohol intoxication found that the magnitude of these ORs weakened to 1.11 (95% CI = 1.04–1.18) when using random-effects and to 1.18 (95% CI = 1.07–1.30) when using PEESE; by contrast, an analysis that did not account for alcohol intoxication found that the ORs were 1.79 (95% CI = 1.28–2.51) and 1.69 (95% CI = 1.25–2.28), respectively.

Primary Literature

The committee did not identify any relevant, good-quality primary literature that reported on the association between cannabis use and motor vehicle crashes and were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question. Of the three identified papers with publication dates during or after 2015 that were not included in Rogeberg and Elvik (2016), none contributed new data on the association between DUIC and MVC risk (Allen et al., 2016; Lemos et al., 2015; Meibodi et al., 2015).

Discussion of Findings

Two important methodological limitations of Rogeberg and Elvik (2016) were noted by other researchers (Gjerde and Morland, 2016). First, DUIC may have not just referred to acute intoxication. Indeed, many of the studies considered in this review scored case and control counts as positive using criteria that would also be satisfied by drivers with recent or regular cannabis use but who were neither intoxicated nor impaired while driving (Gjerde and Morland, 2016). Moreover, the association between THC levels in blood and either acute intoxication or driving impairment remains a subject of controversy, and it could represent an important limitation in the interpretation of findings in culpability studies based on blood THC levels (Desrosiers et al., 2014; Khiabani et al., 2006; Logan et al., 2016; Menetrey et al., 2005; Papafotiou et al., 2005). Second, 3 of the 21 studies used different methods to assess cases and controls, which may lead to a non-differential misclassification of exposure. A missing component in this review is a better determination of the dose

at which driving becomes sufficiently unsafe as to increase MVC risk. Finally, Rogeberg and Elvik (2016) did not provide evidence from cohort studies to address DUIC in MVC.

Simulator studies were also not included in Rogeberg and Elvik (2016). Some laboratory and simulator studies that have examined the effects of acute cannabis intoxication on driving performance have found that the psychomotor skills necessary for safe driving become increasingly impaired at higher doses of cannabis (Sewell et al., 2009). While these experiments may have high internal validity regarding dose-related effects on psychomotor performance, they do not necessarily reflect the complex nature of driving ability and MVC risk attributed to DUIC in a real-world scenario. Epidemiological studies of MVC in populations may help to address these limitations and are the only reasonable and ethical alternative to controlled experiments outside the laboratory. However, cannabis smokers have demographic characteristics that are similar to those of other groups with a high crash risk, including youth, males, and those with a high prevalence of drugged and drunk driving (Bergeron and Paquette, 2014; Richer and Bergeron, 2009). In particular, confounding or effect modification with alcohol is an important driver-related factor that needs to be better taken into account. The bulk of the evidence available describing the association between DUIC and MVCs comes from case-control studies that evaluate the odds of a MVC by DUIC status and from culpability studies which evaluate the odds of culpability in drivers involved in collisions by DUIC status.

CONCLUSION 9-3 There is substantial evidence of a statistical association between cannabis use and increased risk of motor vehicle crashes.

OVERDOSE INJURIES AND DEATH

According to the American Association of Poison Control Centers (AAPCC), 2,047 calls to poison control centers in the United States made in 2014 were in response to single-substance exposures to cannabis, up from 1,548 such exposures in 2013 (Mowry et al., 2014, 2015). Of these exposures, 37 were classified as having major effects, and death was the outcome in 1 (Mowry et al., 2015).⁷ However, these data do not account for overdose injuries or deaths that did not prompt calls to poison con-

⁷ Major effects are defined as those that are “life-threatening or [that] resulted in significant residual disability or disfigurement” (Mowry et al., 2015, p. 1125). Exposures classified as resulting in death are those where “the patient died as a result of the exposure or as a direct complication of the exposure” (Mowry et al., 2015, p. 1125).

tol centers. Data from the Wide-ranging Online Data for Epidemiologic Research (WONDER) database of the Centers for Disease Control and Prevention indicate that in 2014 there were 16,822 deaths in the United States due to accidental poisoning by and exposure to narcotics and psychodysleptics—a broad category that includes cannabis as well as cocaine, heroin, codeine, morphine, and several other narcotics (CDC, 2016b; WHO, 2016). Due, in part, to the limitations of current surveillance tools and medical record coding systems, there is a limited amount of more comprehensive and precise data on the association between cannabis use and overdose injury or death.

Meanwhile, the increasing availability, diversity, and potency of cannabis products create the potential for an increased risk of adverse health effects related to cannabis use, including overdose injury and death. Accidental ingestion of cannabis by young children can result in respiratory failure and coma, as noted by several case reports (Amirav et al., 2011; Appelboam and Oades, 2006; Carstairs et al., 2011), and the consumption of cannabis edibles has been identified as a contributing factor in the accidental death of at least one adolescent (Hancock-Allen et al., 2015).

Thus, the emerging cannabis products market creates the potential for an increased risk of cannabis-related overdose injury or death, while limitations in the current clinical and public health surveillance system hinder efforts to detect, characterize, and respond to this population health issue. This section reviews the available evidence on the association between cannabis use and overdose injury and death and discusses possible actions to improve the state of research on this health endpoint.

Is There an Association Between Cannabis Use and Overdose Injuries or Death?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and overdose injuries or death.

Primary Literature

The committee identified a number of studies that directly or indirectly reported on the association between acute cannabis intoxication and overdose death in either adults or children. An analysis of the National Poison Data Systems database involving more than 2 million human exposure cases in 2012 did not list cannabis among the top causes of death related to pharmaceutical products (Dart et al., 2015). According

to AAPCC annual reports, among all calls to U.S. poison centers involving single-substance exposures to cannabis, death was the outcome in two cases in 2012, no cases in 2013, and one case in 2014 (Mowry et al., 2013, 2014, 2015), although the reports do not indicate whether cannabis exposure was a contributing factor in these outcomes. Cannabis was not found to be the main cause of death in any of the fatal intoxications among drug addicts submitted for medico-legal autopsy and toxicological analysis in Denmark, Finland, Iceland, Norway, or Sweden in either 2007 or 2012 (Simonsen et al., 2011, 2015). Nonetheless, tetrahydrocannabinol was commonly identified (21 percent to 38 percent of cases) in the blood samples of these fatal intoxications.

Case reports on cannabis-related deaths are also uncommon. In Colorado, cannabis intoxication was determined to be a chief contributing factor in the death by trauma of a teenager who jumped from a fourth-floor balcony after ingesting a cookie containing 65 mg of THC (Hancock-Allen et al., 2015). Postmortem analyses revealed no evidence of poly-substance abuse and a delta-9 carboxy-THC whole blood concentration of 49 ng/ml—almost nine times the legal limit for driving in Colorado. Colorado law states that a single-serving edible cannabis product should contain no more than 10 mg of THC; however, currently available edible cannabis products such as cookies and brownies, which are otherwise generally understood as single-serving products, may contain as much as 100 mg (or 10 servings) of THC.⁸ In a study on unintentional pediatric cannabis exposure, Wang et al. (2016) described a case where hospital staff members were unable to resuscitate an unresponsive 11-month-old child who presented with tachycardia and metabolic acidosis and who tested positive for THC in a urine drug screen. The authors noted that any relationship between cannabis exposure and the patient's symptoms or outcome was unclear. Although presented here for discussion, these case reports did not inform the committee's conclusions on the association between cannabis use and overdose death.

By comparison with the minimal literature on cannabis-related overdose death in adults or children, several studies reported on potentially serious symptoms associated with cannabis exposure in pediatric populations. Le Garrec et al. (2014) reported that, over a 3.5-year period, seven children ages 11 to 33 months were admitted to a pediatric intensive care unit in Paris with accidental cannabis poisoning. All of the children had central nervous system symptoms, including drowsiness and coma, and three were intubated and placed on mechanical ventilation for less than 24 hours. Between 2010 and 2013, an Arizona poison control center received

⁸ Colorado Code of Regulations. Department of Revenue. Marijuana Enforcement Division. Retail Marijuana Rules. 1 CCR 212-2 R604 (C5) (2).

49 calls related to unintentional medical marijuana ingestions among children ages 7 years and younger (Lovecchio and Heise, 2015). Among the 39 records with complete information, the most commonly reported symptoms were lethargy (48 percent of cases), an inability to walk (53 percent), coma (10 percent), and vomiting (21 percent). These and other symptoms, including respiratory depression and aspiration pneumonia, underscore the importance of observation in children suspected or known to have unintentionally ingested cannabis. Although presented here for discussion, these case series were published as letters in scientific journals and therefore did not inform the committee's conclusions on the association between cannabis use and overdose injuries.

These findings are supported by retrospective reviews and cohort studies. Wang et al. (2013) retrospectively reviewed cases of unintentional cannabis ingestions among children ages 11 and younger who required medical attention at a children's hospital in Colorado between 2005 and 2011. Out of 1,378 unintentional ingestions, only 14 were cannabis related, of which 13 were observed in the emergency room or admitted to the hospital. Symptoms included lethargy, ataxia, dizziness, and respiratory insufficiency. The proportion of unintentional ingestions that were cannabis related increased from 0 percent in 2005–2009 to 2.4 percent in 2009–2013, a statistically significant increase coinciding with the October 2009 decision by the U.S. Department of Justice to no longer prosecute users and suppliers of cannabis who act in accordance with state laws. In a subsequent study, Wang et al. (2016) reported the prevalence of unintentional pediatric cannabis exposures occurring between 2009 and 2015 at a children's hospital and a poison center in Colorado. The average number of cannabis-related calls per 1,000 calls to the poison center increased significantly from 0.9 in 2012–2013 to 2.3 in 2014–2015, periods corresponding to the 2 years before and after legalization of recreational cannabis in Colorado. Between these same periods, the average number of cannabis-related emergency department visits per 1,000 visits also increased, though nonsignificantly, from 4.3 to 6.4. Symptoms reported in the 163 calls received by the poison center included drowsiness and/or lethargy (49 percent of cases), ataxia and/or dizziness (12 percent), and agitation (8 percent). Out of 81 cases received by the children's hospital, 40 percent were observed in the emergency department, 22 were admitted to an inpatient ward or the intensive care unit, and 2 required respiratory support. Onders et al. (2016) reviewed data from the National Poison Data System and found that between 2000 and 2013, U.S. poison centers received 1,969 calls related to cannabis exposure among children younger than 6 years old. Most exposures were unintentional (92.2 percent) and occurred as a result of ingesting cannabis or a cannabis product (75.0 percent). Drowsiness and/or lethargy accounted for nearly half of reported

clinical symptoms (45.5 percent), while more serious effects, including coma (0.9 percent), cardiovascular symptoms (4.1 percent), and respiratory depression (0.7 percent), occurred less frequently. The annual rate of exposures increased over time, from a national average of 4.21 per million children in 2006 to 10.42 per million children in 2013, corresponding to a statistically significant increase of 147.5 percent. During the same period, the increase in the annual rate of exposures among states that had legalized medical cannabis prior to 2000 was significant, at 609.6 percent.

Collectively, these findings indicate that state-based legalization of cannabis is associated with a subsequent increase in pediatric cannabis exposures in those states. A similar trend emerges when comparing exposure rates among states where cannabis is legal to exposure rates in states where it is not. Wang et al. (2014) reported that between 2005 and 2011 the rate of calls to poison centers for unintentional pediatric cannabis exposures did not increase in states where cannabis remained illegal as of 2012; increased by 11.5 percent (95% CI = -0.4 – 24.7) in states where legislation to legalize cannabis was passed between 2005 and 2011; and increased by 30.3 percent (95% CI = 22.5 – 38.5) in states where cannabis was legalized before 2005. Among children unintentionally exposed to cannabis, those living in states where cannabis was legalized before 2005 were more likely to be evaluated in a health care facility (OR, 1.9, 95% CI = 1.5 – 2.6), to experience major or moderate effects (OR, 2.1, 95% CI = 1.4 – 3.1), and to be admitted to critical care units (OR, 3.4, 95% CI = 1.8 – 6.5) as compared to those living in states where cannabis remained illegal as of 2012. Accounting for 78 percent of all incidents, ingestion was the most common route of unintentional pediatric exposure. Onders et al. (2016) reported that between 2000 and 2013 the annual rate of poison center calls related to cannabis exposures among children younger than 6 was 2.82 times higher in states that had legalized medical cannabis prior to 2000 than in states where medical cannabis remained illegal as of 2013. Another study found that the mean number of calls to poison control centers for unintentional pediatric cannabis exposures increased by 34 percent per year between 2009 and 2015—a significant increase that was also significantly greater than the 19 percent annual increase in cannabis-related calls received by poison control centers throughout the rest of the United States during that same period (Wang et al., 2016). Informed, in part, by these and other findings, a special committee of the Colorado Department of Public Health and Environment found moderate evidence that more unintentional pediatric cannabis exposures have occurred in states with increased legal access to cannabis and that the exposures can lead to significant clinical effects requiring medical attention (CDPHE, 2015).

Discussion of Findings

The committee identified few studies that report on the association between cannabis use and overdose death. Cannabis was not identified as a main cause in the intoxication deaths of drug addicts in five Nordic countries or a top cause of U.S. deaths related to pharmaceutical products. However, studies on the risks to Nordic populations posed by cannabis products available in those countries may not reflect the risks to U.S. populations posed by domestically available cannabis products, and cannabis might still be associated with overdose deaths without also being a top cause among pharmaceutical-related exposure deaths. Data from the National Poison Data System indicate that death was the outcome in a small number of single-substance exposures to cannabis; however, lacking further information, it is not possible to determine whether and to what extent cannabis contributed to these deaths. Case reports implicate acute cannabis intoxication in one accidental death and suggest that cannabis use may pose a risk for sudden cardiac death. However, these individual case reports cannot be used to infer a general association between cannabis use and overdose deaths. Overall, the committee identified no study in which cannabis was determined to be the direct cause of overdose death.

Several studies report that unintentional pediatric cannabis exposure is associated with potentially serious symptoms, including respiratory depression or failure, tachycardia and other cardiovascular symptoms, and temporary coma. Similar symptoms were not reported in adults exposed to cannabis. Most study limitations were related to the origin, quality, and completeness of data. For example, Wang et al. (2013) noted that findings based on data from a single children's hospital or regional poison centers may not be generalizable to other health care facilities or poison centers, especially those in areas where laws regarding cannabis use are different than in Colorado. Search strategies employed in retrospective reviews of records from hospitals and poison centers may fail to capture all pertinent records, and some records may be incomplete (Wang et al., 2016). Data from poison centers will capture only the subset of cannabis-related overdose injuries or deaths that resulted in a call to a poison center and may overrepresent serious cases or cases from states where cannabis is legal (Wang et al., 2014). Moreover, Onders et al. (2016) observed that cannabis exposures are not identical to poisonings and overdoses; consequently, data on trends in cannabis exposures do not necessarily allow for an estimation of trends in cannabis overdose or poisoning.

CONCLUSION 9-4

9-4(a) There is insufficient evidence to support or refute a statistical association between cannabis use and death due to cannabis overdose.

9-4(b) There is moderate evidence of a statistical association between cannabis use and increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal.

RESEARCH GAPS

To address the research gaps relevant to injury and death, the committee suggests the following:

- There is a need for long-term, well-designed cohort studies to determine the association between cannabis use and all-cause and cause-specific mortality among large, representative populations. These studies will need to assess the effects of the various characteristics of cannabis use (e.g., frequency, duration, cumulative exposure) on mortality among demographic and clinical subgroups of interest, to use credible measures of cannabis exposure, and to control for known confounders.
- The association between cannabis use and occupational injury needs to be explored across a broad range of regions, populations, workplace settings, workplace practices (e.g., drug use prevention programs, safety standards), worker characteristics (e.g., medical history, history of drug and alcohol use), work patterns, and occupations.
- There is a need for research to evaluate whether and how the form of cannabis (e.g., edibles, flower, concentrates) affects the risk of overdose and to characterize the incidence and prevalence of overdose deaths in children and adults due to accidental or intentional exposure to edible cannabis.
- There is a need for well-designed surveillance studies to determine the prevalence of acute cannabis use and intoxication among U.S. drivers. Research is also needed to explore how patterns of cannabis use, the degree of acute cannabis intoxication, and geographic and demographic variables affect MVC incidence, driver and passenger outcomes, and driver safety and performance. Finally, research is needed to identify the causal channels through

which cannabis use may adversely or therapeutically affect MVC risk.

- There is a need for research on the association between cannabis use and injury and mortality among unstudied and understudied demographic groups, such as minority groups, working adolescents, and employed older populations.

SUMMARY

This chapter discussed the associations between cannabis use and all-cause mortality, occupational injury, motor vehicle crash, and death and injury due to overdose. Box 9-1 provides a summary of the conclusions from this chapter. Notably, the committee found substantial evidence of a statistical association between cannabis use and motor vehicle crashes. These findings suggest the need for research to further specify the strength of this association and to identify any mediating factors, as well as the need for broader surveillance efforts to track patterns of cannabis use, especially where cannabis use may pose risks to personal and public health.

BOX 9-1

Summary of Chapter Conclusions*

There is substantial evidence of a statistical association between cannabis use and:

- Increased risk of motor vehicle crashes (9-3)

There is moderate evidence of a statistical association between cannabis use and:

- Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal (9-4b)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- All-cause mortality (self-reported cannabis use) (9-1)
- Occupational accidents or injuries (general, nonmedical cannabis use) (9-2)
- Death due to cannabis overdose (9-4a)

* Numbers in parentheses correspond to chapter conclusion numbers.

Apart from illuminating potential research objectives, these findings also suggest enacting policies such as making DUIC a direct target for both policy and policing. Such efforts could include checkpoints for DUIC in conjunction with those for sobriety, the development of point-of-care kits for DUIC testing, and a consideration of zero tolerance laws. These proposals find parallels in policies that restrict or prohibit the use of alcohol while driving, and there is both domestic and international precedent for policing the use of cannabis while operating motor vehicles. In Colorado and Washington, an individual whose blood contains 5 ng/ml or more of THC while driving is considered to be under the influence and is guilty of DUIC.⁹ In Australia, it is illegal to drive with any level of THC in oral fluid or blood samples (Boorman and Owens, 2009).¹⁰ Some research suggests that policies that legalize cannabis for medical use have been associated with a decrease in the incidence of MVC. For example, an ecological study found a net reduction in traffic crashes associated with the introduction of laws for medical cannabis use (Anderson et al., 2013).

The committee also found moderate evidence of a statistical association between cannabis use and an increased risk of overdose injuries among pediatric populations in states in where cannabis is legal. The potential risks associated with the use of highly potent cannabis products suggest a need for public health policies, such as regulations that require packaging for cannabis products to include child-focused safety features, warnings that ingested cannabis can have different effects from smoked cannabis, and guidance on how to respond to potential emergencies. Again, precedents for such policies exist. For example, Colorado regulations require that medical and retail cannabis products be sold in packages that are child-resistant, that list the potency of the product in mg of THC and cannabidiol, and that contain several warning statements, including the direction to keep the product out of the reach of children.^{11,12}

The available evidence was insufficient to draw any conclusions regarding the association between cannabis use and occupational injury or all-cause mortality. The high economic and social costs associated with occupational injuries in this country suggest the need for further research to determine whether these injuries are associated with cannabis use. In pursuing this research, it will be important to determine which individual and work-related factors protect against, or expose workers to, the risk of injury. Emerging evidence suggests that access to legal cannabis can

⁹ Wash. Rev. Code Ann. § 46.61.502 (1) (b). Colo. Rev. Stat. Ann. § 42-4-1301 (6) (a) (IV).

¹⁰ Road Traffic Act 1974, Part V, Division 2, Section 64AC (1).

¹¹ Colorado Code of Regulations. Department of Revenue. Marijuana Enforcement Division. Medical Marijuana Rules. 1 CCR 212-1 M1004.5 (B) and M1005 (B).

¹² Colorado Code of Regulations. Department of Revenue. Marijuana Enforcement Division. Retail Marijuana Rules. 1 CCR 212-2 R1006 (A-B).

increase the incidence of accidental cannabis ingestion among pediatric populations and that such ingestion can lead to depressed respiratory function and other symptoms of overdose. If state-level changes in cannabis policy continue to make cannabis more accessible, there will be an increased need for research to assess the prevalence of injuries and death due to cannabis overdose, especially among children and other vulnerable populations.

REFERENCES

- Allen, J. A., K. C. Davis, J. C. Duke, J. M. Nonnemaker, B. R. Bradfield, M. C. Farrelly, S. P. Novak, and G. A. Zarkin. 2016. Association between self-reports of being high and perceptions about the safety of drugged and drunk driving. *Health Education Research* 31(4):535–541.
- Amirav, I., A. Luder, Y. Viner, and M. Finkel. 2011. Decriminalization of cannabis—potential risks for children? *Acta Paediatrica* 100(4):618–619.
- Anderson, D. M., B. Hansen, and D. I. Rees. 2013. Medical marijuana laws, traffic fatalities, and alcohol consumption. *The Journal of Law and Economics* 56(2):333–369.
- Andreasson, S., and P. Allebeck. 1990. Cannabis and mortality among young men: A longitudinal study of Swedish conscripts. *Scandinavian Journal of Social Medicine* 18(1):9–15.
- Appelboom, A., and P. J. Oades. 2006. Coma due to cannabis toxicity in an infant. *European Journal of Emergency Medicine* 13(3):177–179.
- Asbridge, M., J. A. Hayden, and J. L. Cartwright. 2012. Acute cannabis consumption and motor vehicle collision risk: Systematic review of observational studies and meta-analysis. *BMJ* 344:e536.
- Azofeifa, A., M. E. Mattson, and R. Lyerla. 2015. Driving under the influence of alcohol, marijuana, and alcohol and marijuana combined among persons aged 16–25 years—United States, 2002–2014. *Morbidity and Mortality Weekly Report* 64(48):1325–1329.
- Azofeifa, A., M. E. Mattson, G. Schauer, T. McAfee, A. Grant, and R. Lyerla. 2016. National estimates of marijuana use and related indicators—National Survey on Drug Use and Health, United States, 2002–2014. *Morbidity and Mortality Weekly Report Surveillance Summaries* 65(11):1–28.
- Bedard, M., S. Dubois, and B. Weaver. 2007. The impact of cannabis on driving. *Canadian Journal of Public Health* 98(1):6–11.
- Bergen, G., C. Peterson, D. Ederer, C. Florence, T. Haileyesus, M. J. Kresnow, and L. Xu. 2014. Vital signs: Health burden and medical costs of nonfatal injuries to motor vehicle occupants—United States, 2012. *Morbidity and Mortality Weekly Report* 63(40):894–900.
- Bergeron, J., and M. Paquette. 2014. Relationships between frequency of driving under the influence of cannabis, self-reported reckless driving and risk-taking behavior observed in a driving simulator. *Journal of Safety Research* 49:19–24.
- Berning, A., R. Compton, and K. Wochinger. 2015. Results of the 2013–2014 national roadside survey of alcohol and drug use by drivers. *Traffic Safety Facts Research Note*. Report No. DOT HS 812 118. Washington, DC: National Highway Traffic Safety Administration.
- BLS (Bureau of Labor Statistics). 2015. *Employer-reported workplace injuries and illnesses—2014*. Report No. USDL-15-2086. Washington, DC: Bureau of Labor Statistics. https://www.bls.gov/news.release/archives/osh_10292015.pdf (accessed November 16, 2016).
- BLS. 2016. *Injuries, illnesses, and fatalities: Revisions to the 2014 census of fatal occupational injuries (CFOI)*. http://www.bls.gov/iif/cfoi_revised14.htm (accessed November 16, 2016).

- Boorman, M., and K. Owens. 2009. The Victorian legislative framework for the random testing drivers at the roadside for the presence of illicit drugs: An evaluation of the characteristics of drivers detected from 2004 to 2006. *Traffic Injury Prevention* 10(1):16–22.
- Calabria, B., L. Degenhardt, W. Hall, and M. Lynskey. 2010. Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. *Drug and Alcohol Review* 29(3):318–330.
- Carstairs, S. D., M. K. Fujinaka, G. E. Keeney, and B. T. Ly. 2011. Prolonged coma in a child due to hashish ingestion with quantitation of the metabolites in urine. *Journal of Emergency Medicine* 41(3):e69–e71.
- CBHSQ (Center for Behavioral Health Statistics and Quality). 2016. *2015 national survey on drug use and health: Detailed tables*. <http://www.samhsa.gov/data/sites/default/files/NSDUH-DefTabs-2015/NSDUH-DefTabs-2015/NSDUH-DefTabs-2015.pdf> (accessed December 27, 2016).
- CDC (Centers for Disease Control and Prevention). 2015. *State-specific costs of motor vehicle crash deaths*. <https://www.cdc.gov/motorvehiclesafety/statecosts/index.html> (accessed October 18, 2016).
- CDC. 2016a. *WISQARS: Nonfatal injury reports, 2001–2014*. <http://webappa.cdc.gov/sasweb/ncipc/nfirates2001.html> (accessed October 18, 2016).
- CDC. 2016b. *WONDER: About underlying cause of death, 1999–2014*. <https://wonder.cdc.gov/ucd-icd10.html> (accessed October 18, 2016).
- CDPHE (Colorado Department of Public Health and Environment). 2015. *Monitoring health concerns related to marijuana use in Colorado: 2014*. <http://www2.cde.state.co.us/artemis/hemonos/he1282m332015internet/he1282m332015internet01.pdf> (accessed December 27, 2016).
- Compton, R. P., and A. Berning. 2015. Drug and alcohol crash risk. *Traffic Safety Facts Research Note*. DOT HS 812 117. Washington, DC: National Highway Traffic Safety Administration. http://www.nhtsa.gov/staticfiles/nti/pdf/812117-Drug_and_Alcohol_Crash_Risk.pdf (accessed December 20, 2016).
- Dart, R. C., A. C. Bronstein, D. A. Spyker, L. R. Cantilena, S. A. Seifert, S. E. Heard, and E. P. Krenzlok. 2015. Poisoning in the United States: 2012 Emergency Medicine Report of the National Poison Data System. *Annals of Emergency Medicine* 65(4):416–422.
- Degenhardt, L., H. A. Whiteford, A. J. Ferrari, A. J. Baxter, F. J. Charlson, W. D. Hall, G. Freedman, R. Burstein, N. Johns, R. E. Engell, A. Flaxman, C. J. Murray, and T. Vos. 2013. Global burden of disease attributable to illicit drug use and dependence: Findings from the global burden of disease study 2010. *Lancet* 382(9904):1564–1574.
- Desrosiers, N. A., S. K. Himes, K. B. Scheidweiler, M. Concheiro-Guisan, D. A. Gorelick, and M. A. Huestis. 2014. Phase I and II cannabinoid disposition in blood and plasma of occasional and frequent smokers following controlled smoked cannabis. *Clinical Chemistry* 60(4):631–643.
- Dong, X. S., X. Wang, and J. A. Largay. 2015. Occupational and non-occupational factors associated with work-related injuries among construction workers in the USA. *International Journal of Occupational and Environmental Health* 21(2):142–150.
- Elvik, R. 2013. Risk of road accident associated with the use of drugs: A systematic review and meta-analysis of evidence from epidemiological studies. *Accident Analysis & Prevention* 60:254–267.
- Fransen, M., B. Wilmshire, J. Winstanley, M. Woodward, R. Grunstein, S. Ameratunga, and R. Norton. 2006. Shift work and work injury in the New Zealand blood donors' health study. *Occupational and Environmental Medicine* 63(5):352–358.
- Gjerde, H., and J. Morland. 2016. Risk for involvement in road traffic crash during acute cannabis intoxication. *Addiction* 111(8):1492–1495.

- Hancock-Allen, J. B., L. Barker, M. VanDyke, and D. B. Holmes. 2015. Notes from the field: Death following ingestion of an edible marijuana product—Colorado, March 2014. *Morbidity and Mortality Weekly Report* 64(28):771–772.
- Hartman, R. L., and M. A. Huestis. 2013. Cannabis effects on driving skills. *Clinical Chemistry* 59(3):478–492.
- Hoffmann, J., and C. Larison. 1999. Drug use, workplace accidents and employee turnover. *Journal of Drug Issues* 29(2):341–364.
- Intiaz, S., K. D. Shield, M. Roerecke, J. Cheng, S. Popova, P. Kurdyak, B. Fischer, and J. Rehm. 2016. The burden of disease attributable to cannabis use in Canada in 2012. *Addiction* 111(4):653–662.
- IOM (Institute of Medicine). 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC: National Academy Press.
- Kaestner, R., and M. Grossman. 1995. Wages, workers' compensation benefits, and drug use: Indirect evidence of the effect of drugs on workplace accidents. *American Economic Review* 85(2):55–60.
- Kaestner, R., and M. Grossman. 1998. The effect of drug use on workplace accidents. *Labour Economics* 5(3):267–294.
- Khiabani, H. Z., J. G. Bramness, A. Bjerneboe, and J. Morland. 2006. Relationship between THC concentration in blood and impairment in apprehended drivers. *Traffic Injury Prevention* 7(2):111–116.
- Le Garrec, S., S. Dauger, and P. Sachs. 2014. Cannabis poisoning in children. *Intensive Care Medicine* 40(9):1394–1395.
- Leigh, J. P. 2011. Economic burden of occupational injury and illness in the United States. *Milbank Quarterly* 89(4):728–772.
- Lemos, N. P., A. C. San Nicolas, J. A. Volk, E. A. Ingle, and C. M. Williams. 2015. Driving under the influence of marijuana versus driving and dying under the influence of marijuana: A comparison of blood concentrations of delta9-tetrahydrocannabinol, 11-hydroxy-delta9-tetrahydrocannabinol, 11-nor-9-carboxy-delta9-tetrahydrocannabinol and other cannabinoids in arrested drivers versus deceased drivers. *Journal of Analytical Toxicology* 39(8):588–601.
- Li, M. C., J. E. Brady, C. J. DiMaggio, A. R. Lusardi, K. Y. Tzong, and G. Li. 2012. Marijuana use and motor vehicle crashes. *Epidemiologic Reviews* 34:65–72.
- Logan, B., S. L. Kacinko, and D. J. Beirness. 2016. *An Evaluation of Data from Drivers Arrested for Driving Under the Influence in Relation to Per Se Limits for Cannabis*. AAA Foundation for Traffic Safety: Washington, DC. <https://www.aaafoundation.org/sites/default/files/EvaluationOfDriversInRelationToPerSeReport.pdf> (accessed December 27, 2016).
- Lovecchio, F., and C. W. Heise. 2015. Accidental pediatric ingestions of medical marijuana: A 4-year poison center experience. *American Journal of Emergency Medicine* 33(6):844–845.
- Macdonald, S., W. Hall, P. Roman, T. Stockwell, M. Coghlan, and S. Nesvaag. 2010. Testing for cannabis in the work-place: A review of the evidence. *Addiction* 105(3):408–416.
- Manrique-Garcia, E., A. Ponce de Leon, C. Dalman, S. Andreasson, and P. Allebeck. 2016. Cannabis, psychosis, and mortality: A cohort study of 50,373 Swedish men. *American Journal of Psychiatry* 173(8):790–798.
- Marucci-Wellman, H. R., T. K. Courtney, H. L. Corns, G. S. Sorock, B. S. Webster, R. Wasiak, Y. I. Noy, S. Matz, and T. B. Leamon. 2015. The direct cost burden of 13 years of disabling workplace injuries in the U.S. (1998–2010): Findings from the Liberty Mutual workplace safety index. *Journal of Safety Research* 55:53–62.
- Meibodi, M. K., S. Esfandyari, V. Siyabi, and S. Roosta. 2015. Illicit drug abuse in drivers of motor vehicle collisions. *Galen Medical Journal* 4(1):39–46.

- Menetrey, A., M. Augsburger, B. Favrat, M. A. Pin, L. E. Rothuizen, M. Appenzeller, T. Buclin, P. Mangin, and C. Giroud. 2005. Assessment of driving capability through the use of clinical and psychomotor tests in relation to blood cannabinoids levels following oral administration of 20 mg dronabinol or of a cannabis decoction made with 20 or 60 mg delta9-THC. *Journal of Analytical Toxicology* 29(5):327–338.
- Mowry, J. B., D. A. Spyker, L. R. Cantilena, Jr., J. E. Bailey, and M. Ford. 2013. 2012 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th annual report. *Clinical Toxicology* 51(10):949–1229.
- Mowry, J. B., D. A. Spyker, L. R. Cantilena, Jr., N. McMillan, and M. Ford. 2014. 2013 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st annual report. *Clinical Toxicology* 52(10):1032–1283.
- Mowry, J. B., D. A. Spyker, D. E. Brooks, N. McMillan, and J. L. Schauben. 2015. 2014 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 32nd annual report. *Clinical Toxicology* 53(10):962–1147.
- Muhuri, P. K., and J. C. Gfroerer. 2011. Mortality associated with illegal drug use among adults in the United States. *American Journal of Drug and Alcohol Abuse* 37(3):155–164.
- NHTSA (National Highway Traffic Safety Administration). 2015. *Motor vehicle traffic crashes as a leading cause of death in the United States, 2010 and 2011*. <https://crashstats.nhtsa.dot.gov/Api/Public/ViewPublication/812203> (accessed December, 27, 2016).
- NHTSA. 2016. *Fatality Analysis Reporting System (FARS) encyclopedia*. <http://www-fars.nhtsa.dot.gov/Main/index.aspx> (accessed December 27, 2016).
- NRC and IOM (National Research Council and Institute of Medicine). 1994. *Under the influence?: Drugs and the American work force*. Washington, DC: National Academy Press.
- Onders, B., M. J. Casavant, H. A. Spiller, T. Chounthirath, and G. A. Smith. 2016. Marijuana exposure among children younger than six years in the United States. *Clinical Pediatrics* 55(5):428–436.
- Papafotiou, K., J. D. Carter, and C. Stough. 2005. The relationship between performance on the standardised field sobriety tests, driving performance and the level of delta9-tetrahydrocannabinol (THC) in blood. *Forensic Science International* 155(2–3):172–178.
- Price, J. W. 2014. Marijuana and workplace safety: An examination of urine drug tests. *Journal of Addictive Diseases* 33(1):24–27.
- Richer, I., and J. Bergeron. 2009. Driving under the influence of cannabis: Links with dangerous driving, psychological predictors, and accident involvement. *Accident Analysis & Prevention* 41(2):299–307.
- Rogeberg, O., and R. Elvik. 2016. The effects of cannabis intoxication on motor vehicle collision revisited and revised. *Addiction* 111(8):1348–1359.
- Sewell, R. A., J. Poling, and M. Sofuoglu. 2009. The effect of cannabis compared with alcohol on driving. *American Journal on Addictions* 18(3):185–193.
- Shipp, E. M., S. R. Tortolero, S. P. Cooper, E. G. Baumler, and N. F. Weller. 2005. Substance use and occupational injuries among high school students in South Texas. *American Journal of Drug and Alcohol Abuse* 31(2):253–265.
- Sidney, S., J. E. Beck, I. S. Tekawa, C. P. Quesenberry, and G. D. Friedman. 1997. Marijuana use and mortality. *American Journal of Public Health* 87(4):585–590.
- Simonsen, K. W., P. T. Normann, G. Ceder, E. Vuori, S. Thordardottir, G. Thelander, A. C. Hansen, B. Teige, and D. Rollmann. 2011. Fatal poisoning in drug addicts in the Nordic countries in 2007. *Forensic Science International* 207(1-3):170–176.
- Simonsen, K. W., H. M. Edvardson, G. Thelander, I. Ojanpera, S. Thordardottir, L. V. Andersen, P. Kriikku, V. Vindenes, D. Christoffersen, G. J. Delaveris, and J. Frost. 2015. Fatal poisoning in drug addicts in the Nordic countries in 2012. *Forensic Science International* 248:172–180.

- Wadsworth, E. J., S. C. Moss, S. A. Simpson, and A. P. Smith. 2006. A community based investigation of the association between cannabis use, injuries and accidents. *Journal of Psychopharmacology* 20(1):5–13.
- Wang, G. S., G. Roosevelt, and K. Heard. 2013. Pediatric marijuana exposures in a medical marijuana state. *JAMA Pediatrics* 167(7):630–633.
- Wang, G. S., G. Roosevelt, M. C. Le Lait, E. M. Martinez, B. Bucher-Bartelson, A. C. Bronstein, and K. Heard. 2014. Association of unintentional pediatric exposures with decriminalization of marijuana in the United States. *Annals of Emergency Medicine* 63(6):684–689.
- Wang, G. S., M. C. Le Lait, S. J. Deakne, A. C. Bronstein, L. Bajaj, and G. Roosevelt. 2016. Unintentional pediatric exposures to marijuana in Colorado, 2009–2015. *JAMA Pediatrics* 170(9):e160971.
- WHO (World Health Organization). 2016. Accidental poisoning by and exposure to noxious substances (X40-X49). *ICD-10 Version: 2015*. <http://apps.who.int/classifications/icd10/browse/2015/en#!/X40-X49> (accessed November 30, 2016).
- Zwerling, C., J. Ryan, and E. J. Orav. 1990. The efficacy of preemployment drug screening for marijuana and cocaine in predicting employment outcome. *JAMA* 264(20):2639–2643.

10

Prenatal, Perinatal, and Neonatal Exposure to Cannabis

Chapter Highlights

- Smoking cannabis during pregnancy is linked to lower birth weight in the offspring.
- The relationship between smoking cannabis during pregnancy and other pregnancy and childhood outcomes is unclear.

The issue of exposure to cannabis during pregnancy reflects concerns that two different individuals may experience the potential adverse effects of cannabis, which is the illicit drug used most frequently by women of childbearing age. The Substance Abuse and Mental Health Services Administration's National Survey on Drug Use and Health found that in 2015, 3.4 percent of pregnant women ages 15 to 44 had used marijuana during the previous month (CBHSQ, 2016). This is compared to 0.8 percent of pregnant women who used pain relievers, the next most used illicit drug among pregnant women (CBHSQ, 2016). In part because cannabis is an illicit drug, there is very little information on the physiological effects of cannabis in pregnancy on the mother. Moreover, most of the data reflect cannabis administered by smoking and not cannabis exposure through other routes of administration.

Concern about the fetus and newborn stems from the fact that tetrahydrocannabinol (THC) crosses the placenta (Bailey et al., 1987). A rapidly

growing body of evidence indicates that endocannabinoids play roles in a broad array of critical neurodevelopmental processes, from early neural stem cell survival and proliferation to the migration and differentiation of both glial and neuronal lineages as well as neuronal connectivity and synaptic function (Lubman et al., 2014). Another potentially important issue is that THC is secreted in breast milk and can accumulate to high concentrations (Garry et al., 2009).

This chapter focuses on exposure to cannabis from the beginning of pregnancy through the infant's first month of life. Thus, the review covers complications of pregnancy, fetal effects, exposure through breast milk, and later effects of fetal exposure. Although the general principle of the overall report is to restrict the literature reviewed to that which has emerged since the publication of *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999), the last Institute of Medicine report on marijuana, the committee chose to include information concerning longer-term outcomes from two older cohorts released in the 1980s, with the rationale that the identification of late adolescent and young adult outcomes would require that length of follow-up. The committee hand-searched additional literature to examine other prioritized long-term health outcomes not covered in these cohort studies.

The committee identified only one recent good- to fair-quality systematic review (Gunn et al., 2016). This review sought information on a comprehensive set of complications of pregnancy and on fetal and neonatal outcomes up to 6 weeks postpartum. Several lower-quality systematic reviews (Fryers and Brugha, 2013; Irner, 2012; Savitz and Murnane, 2010; Williams and Ross, 2007), narrative reviews (Andrade, 2016; Forray et al., 2015; Hashibe et al., 2005; Huang et al., 2015; Huizink, 2014; Metz and Stickrath, 2015; Schempf, 2007; Viteri et al., 2015), and articles from the grey literature (CDPHE, 2015) were used to identify outcomes not reviewed in Gunn et al. (2016), as was a bibliographic search of materials published from 1999 onward. A literature search was also conducted for outcomes in Gunn et al. (2016), from 2014 to August 2016, to identify any more recent articles. The committee identified 30 primary literature articles that best address the committee's research questions of interest.

PREGNANCY COMPLICATIONS FOR THE MOTHER

Is There an Association Between Cannabis Use and Pregnancy Complications for the Mother?

Stillbirth and Spontaneous Abortion

Systematic Reviews The committee did not identify a good- to fair-quality systematic review that reported on the association between cannabis exposure and stillbirth or spontaneous abortion.

Primary Literature Varner et al. (2014) used results from a population-based case-control study conducted by the Stillbirth Collaborative Research Network to compare illicit drug use in pregnancies that did and did not result in stillbirth.¹ Among 663 stillbirth deliveries, women who had a stillbirth were twice as likely as those with a live birth to report having been addicted to an illicit drug. Tetrahydrocannabinolic acid (THCA), the most common individual drug reported by the population, was found in 2.9 percent of women with a stillbirth and 1.7 percent of the controls (odds ratio [OR] for stillbirth, 2.34; 95% confidence interval [CI] = 1.13–4.81). However, the authors indicate that the result may have been partially confounded by exposure to cigarette smoking and that they may not have had the statistical power to disentangle this effect.

Warshak et al.'s 2015 study on the association between marijuana exposure and adverse neonatal outcomes included stillbirth in the outcomes they examined and found no association (1.1 percent among 361 cannabis users versus 1.5 percent among 6,107 cannabis nonusers; $p = 0.54$).

Fetal Distress

Systematic Reviews Gunn et al. (2016) found no association between marijuana use and fetal distress based on two studies (Berenson et al., 1996; Witter and Niebyl, 1990).

Primary Literature The committee did not identify any good-quality primary literature that reported on the association between cannabis use and fetal distress and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

¹ Fetal death was defined in the study as 20 weeks of gestation or less (Varner et al., 2014).

Other Complications

Systematic Reviews The assessment of the literature on pregnancy complications for the mother relied primarily on Gunn et al. (2016). Of the possible complications, only the increased risk of anemia had a significant association with exposure to cannabis (pooled odds ratio [pOR], 1.36; 95% CI = 1.10–1.69). Mixed findings about an association with cannabis use occurred in studies of precipitate labor and the manual removal of the placenta. No associations were found between in utero exposure to cannabis and the following health outcomes: maternal diabetes, rupture of membranes, premature onset of labor, use of prenatal care, duration of labor, placental abruption, secondary arrest of labor, elevated blood pressure, hyperemesis gravidarum, maternal bleeding after 20 weeks, antepartum or postpartum hemorrhage, maternal weight gain, maternal postnatal issues, duration of maternal hospital stay, or hormone concentrations (Gunn et al., 2016).

Primary Literature Three further studies were identified: Budde et al. (2007), Leemaqz et al. (2016), and Warshak et al. (2015). These studies examined the association between cannabis exposure and the following outcomes: anemia, precipitate labor, manual removal of the placenta, maternal diabetes, rupture of membranes, premature onset of labor, use of prenatal care, duration of labor, secondary arrest of labor, elevated blood pressure, hyperemesis gravidarum, maternal bleeding after 20 weeks, antepartum or postpartum hemorrhage, placental abruption, maternal weight gain, maternal postnatal problems, and duration of maternal hospital stay.

Findings in Leemaqz et al. (2016) from 313 women who used cannabis during pregnancy and Warshak et al. (2015) from 4,892 women who used cannabis during pregnancy were consistent with there being no significant association between cannabis exposure and gestational diabetes (adjusted odds ratio [aOR], 1.11; 95% CI = 0.52–2.38; $p = 0.949$ and aOR, 0.87; 95% CI = 0.66–1.04; $p = 0.04$, respectively) or gestational hypertension/preeclampsia (aOR, 0.443; 95% CI = 0.13–3.54; $p = 0.671$ and aOR, 0.84; 95% CI = 0.68–1.04; $p = 0.12$, respectively). Warshak et al. (2015) did not find a statistically significant association between cannabis use and placental abruption (aOR, 1.17; 95% CI = 0.81–1.70; $p = 0.25$). Budde et al. (2007) reported an increased risk of placental abruption that did not achieve standard statistical significance (OR, 2.83; 95% CI = 0.86–10.78; $p = 0.055$).

Discussion of Findings

Despite identifying one good- to fair-quality systematic review addressing pregnancy complications for the mother, the findings of the review must be interpreted with caution. The review relied on a primary literature that is limited in the number, quality, and rigor of the studies that have been carried out to date. By and large, the existing studies have been retrospective cohort studies, many of which looked at a large number of outcomes without biological plausibility or a biological mechanism guiding the test of the hypothesis. For example, the association identified between anemia and cannabis use in pregnancy arises in the absence of a clear mechanism by which these factors would be related. In addition, many studies were underpowered to detect relatively rare pregnancy complications. Therefore, though Gunn's review reports "no association" for the vast majority of conditions selected, it remains unclear whether this represents a type II error. Ethical challenges obviously preclude the ability to conduct randomized controlled trials of cannabis use in pregnancy, thereby precluding the ability to establish causal relationships. Logistical and financial constraints make even prospective cohort studies of adequate size and duration challenging to fund and implement. Even with rigorous study designs, comorbid tobacco and polysubstance use often confound the interpretation of the data. Such considerations markedly diminish the confidence with which the committee can draw conclusions regarding how much risk can be attributed to cannabis in the area of adverse maternal events.

CONCLUSION 10-1 There is limited evidence of a statistical association between maternal cannabis smoking and pregnancy complications for the mother.

FETAL GROWTH AND DEVELOPMENT**Is There an Association Between Cannabis Use and Fetal Growth and Development?***Birthweight*

Systematic Reviews Studies reviewed in Gunn et al. (2016) that examined the effect of cannabis exposure on birth weight reported both mean birth weights and the percentage of infants at low birth weight (LBW; defined as 2.2kg or 5.5 lbs). Gunn et al. (2016) found that in utero exposure to cannabis is associated with a decrease in birth weight among cannabis-exposed infants (pOR, 1.77; 95% CI = 1.04–3.01; pooled mean difference

[pMD], -109.42 grams; 95% CI = -38.72 to -180.12) compared to those without cannabis exposure.

Primary Literature Similar to the findings reported by Gunn et al. (2016), Gray et al. (2010) and Fergusson et al. (2002) also reported lower mean birth weights for infants prenatally exposed to cannabis. Among 9,521 mothers, Fergusson et al. (2002) showed a -84.20 gram difference (95% CI = -174.7 to -6.4; $p = 0.005$) in birth weight for the children of mothers who had used cannabis at least once per week before and throughout pregnancy versus nonusers. Out of 86 total infants of cannabis-using mothers (independent from tobacco use), Gray et al. (2010) reported a mean birth weight of 3,161 grams (standard deviation [SD], 689; $p = 0.051$) among 41 infants who had been exposed to cannabis and 3,417 grams (SD, 504; $p = 0.051$) among 45 infants who had not been exposed to cannabis. In contrast, Schempf and Strobino (2008) found that, when adjusted for other drug use (i.e., cocaine and opiates), there was no significant association between cannabis use and LBW (defined as less than 2,500 grams) (aOR, 0.93; 95% CI = 0.55–1.57).

Birth Length

Systematic Reviews In their systematic review, Gunn et al. (2016) found that for the nine studies that reported neonatal length at birth (measured in centimeters), there was no statistically significant association between neonatal length and prenatal exposure to cannabis (pMD, -0.10; 95% CI = -0.65–0.45).

Primary Literature Birth length was also examined by Fergusson et al. (2002), who found that children who had been exposed to cannabis in utero had a lower birth length than children who had not been prenatally exposed to cannabis. However, after adjusting for various confounding factors (e.g., cigarette smoking during pregnancy, alcohol consumption during pregnancy), the association was no longer significant ($p = 0.225$). Similarly, Gray et al. (2010) found nonsignificant differences in birth length between 41 infants of cannabis-using mothers (independent from tobacco use) (49.8 cm; SD, 3.8; $p = 0.156$) and 45 infants of non-using mothers (50.8 cm; SD, 2.2; $p = 0.156$).

Head Circumference

Systematic Reviews Gunn et al. (2016) found that among the 10 studies they reviewed that measured head circumference at birth, no statistical

association was found between cannabis exposure in utero and neonatal head circumference (cm) (pMD, -0.31 ; 95% CI = -0.74 – 0.13).

Primary Literature The committee did not identify any good-quality primary literature that reported on the association between cannabis use and head circumference and that was published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Intrauterine Growth Restriction/Small for Gestational Age

There are two ways to describe slower-than-expected growth for a particular duration of gestation. The first is intrauterine growth restriction (IUGR), an obstetric diagnosis based on serial ultrasounds during pregnancy. The second is small for gestational age (SGA), which applies to infants with a birth weight that is less than the 10th or 5th percentile on normative growth curves. The limitation of the latter is that it does not distinguish between those infants with true slow growth and those with normal growth in the lower percentiles.

Systematic Reviews Gunn et al. (2016) addressed two studies that looked at the relationship between in utero cannabis exposure and SGA and concluded that no association can be reported on the association between exposure to cannabis during pregnancy and IUGR/SGA. A pOR was not reported.

Primary Literature Leemaqz et al. (2016) similarly did not find an association between cannabis exposure and SGA (defined as a birth weight less than the 10th percentile) when adjusted for any smoking (aOR, 1.13; 95% CI = 0.80–1.60). In a path analysis of urban black women who reported cannabis use at 50 percent of prenatal visits, Janisse et al. (2014) found a reduction in birth weight for heavy marijuana use alone (-55.2 grams), with a path coefficient of 0.05.² Their analysis suggests that LBW resulting from cannabis exposure reflects fetal growth restriction rather than premature delivery.

Congenital Malformation

In this category the committee considered infants who had malformations or anomalies diagnosed prenatally or after birth. Congenital malformations reflect abnormalities of fetal development in one or more

² The authors used a z-score of birth weight for duration of gestation residualized.

organ systems and can occur throughout pregnancy. They may be identified before or after birth.

Systematic Reviews Gunn et al. (2016) reported no association between cannabis exposure and chromosomal anomalies. No estimate of effect was provided.

Primary Literature Warshak et al. (2015) analyzed data from among 4,892 cannabis users and 153 marijuana cannabis nonusers and reported no association between cannabis exposure and fetal anomalies (aOR, 1.29; 95% CI = 0.87–1.92). In contrast, Forrester and Merz (2006) found higher rates of cannabis use to be associated with the presence of 19 defects out of a total of 54 selected conditions.³ However, this study only performed bivariate comparisons for exposure/no exposure without considering other substances, confounders, or multiple comparisons.

Two case-control studies of the association of cannabis exposure to specific malformations were found. Using data from the National Birth Defects Prevention Study (1997–2005), van Gelder et al. (2014) examined the association between maternal cannabis use from 1 month before pregnancy through the end of the third month of pregnancy and 20 selected anomalies (n = 13,859 case infants; n = 6,556 control infants). The authors reported an increased risk of the following anomalies: anencephaly (aOR, 2.2; 95% CI = 1.3–3.7), esophageal atresia (aOR, 1.4; 95% CI = 0.8–2.4), diaphragmatic hernia (aOR, 1.4; 95% CI = 0.9–2.2), and gastroschisis (aOR, 1.2; 95% CI = 0.9–1.7). Williams et al. (2004) obtained an (aOR, 1.90; 95% CI = 1.29–2.81) for the risk of isolated ventricular septal defect (VSD) among 122 isolated VSD cases and 3,029 control infants.

Discussion of Findings

The findings for birth weight are consistent with the effects of non-cannabinoid substances in smoked cannabis and cigarette smoking. It has been shown in several studies that the increases in carbon monoxide, with elevated carboxyhemoglobin blood levels, may be up to fivefold higher after marijuana than cigarettes (Wu et al., 1988). In other studies of marijuana exposure during pregnancy, the cause of the fetal growth

³ The authors found higher rates of association between cannabis use and the following birth defects: encephalocele, hydrocephaly, microcephaly, anotia/microtia, tetralogy of Fallot, ventricular septal defect, atrial septal defect, pulmonary valve atresia/stenosis, hypoplastic left heart syndrome, cleft palate alone, cleft lip with/without cleft palate, pyloric stenosis, anal/rectal/large-intestinal atresia/stenosis, obstructive genitourinary defect, polydactyly, syndactyly, reduction deformity of upper limbs, gastroschisis, and trisomy 21 (Forrester and Merz, 2006).

restriction noted was proposed to be fetal hypoxia due to the shift in the oxyhemoglobin curve caused by carbon monoxide (Frank et al., 1990).

CONCLUSION 10-2 There is substantial evidence of a statistical association between maternal cannabis smoking and lower birth weight of the offspring.

NEONATAL CONDITIONS

Is There an Association Between Maternal Cannabis Use and Neonatal Conditions in the Infant?

Prematurity/Gestational Age

Systematic Reviews Gunn et al. (2016) documented a decrease in gestational age (measured in weeks) associated with cannabis use (pMD, -0.20 ; 95% CI = -0.62 to -0.22) and increased odds of the risk of preterm delivery (<37 completed weeks) (pOR, 1.29; 95% CI = 0.80–2.08).

Primary Literature Two other studies, Gray et al. (2010) and van Gelder et al. (2014), found no association between cannabis use and shortened gestation. For a total of 86 infants, Gray et al. (2010) reported a median estimated gestational age at delivery of 39 weeks ($p = 0.685$) both for infants who were exposed to cannabis and for infants who were not exposed to cannabis. van Gelder et al. (2014) found no association between cannabis use and gestational age after adjusting for gestational weight gain (aOR, 0.6; 95% CI = 0.1–2.4; $n = 3$ exposed; $n = 335$ nonexposed). The study was likely not to have the power to detect a difference.

Two studies, Dekker et al. (2012) and Leemaqz et al. (2016), reported an increased risk of spontaneous preterm birth associated with cannabis use (aOR, 2.34; 95% CI = 1.22–4.52 and aOR, 2.28; 95% CI = 1.49–3.60; $p < 0.001$, respectively).

Neonatal Intensive Care Unit Admission

Systematic Reviews Gunn et al. (2016) reported increased risk of neonatal intensive care unit (NICU) admission for infants exposed to prenatal cannabis (pOR, 2.02; 95% CI = 1.27–3.21).

Primary Literature Warshak et al. (2015) also found an increased risk of NICU admission among infants born to 4,892 cannabis users and 153 nonusers (aOR, 1.54; 95% CI = 1.14–2.07).

Other Neonatal Conditions

Systematic Reviews Gunn et al. (2016) considered other neonatal conditions and found no association between maternal cannabis use and infant Apgar scores at 1 and 5 minutes. They did not find any differences for jaundice, resuscitation, respiratory distress syndrome, intubation following delivery, hypoglycemia, and sepsis. Studies were mixed as to whether infants exhibited abnormal behavior on neonatal behavioral assessments, in part because different assessment instruments were used in each study.

Primary Literature Warshak et al. (2015) did not find a statistically significant difference in the length of infant hospital stays (aOR, 1.12; 95% CI = 0.95–1.31). Gray et al. (2010) examined Apgar scores at 1 and 5 minutes and found no association between the scores and infant cannabis exposure ($p = 0.709$ and $p = 0.496$, respectively).

Discussion of Findings

The literature with regard to prematurity is mixed and needs further study. No neonatal outcomes appeared to be associated with cannabis exposure, but the studies are limited. Findings related to health care use, such as the increase in NICU admissions, need to be treated with caution. This pattern may reflect protocols requiring admission of all infants whose mothers have a history of substance use in pregnancy or failed toxicological screens during labor, rather than the health of the infant per se, particularly as there appears to be no increase in length of neonatal stay.

CONCLUSION 10-3 There is limited evidence of a statistical association between maternal cannabis smoking and admission of the infant to the neonatal intensive care unit (NICU).

LATER OUTCOMES

Is There an Association Between Maternal Cannabis Use and Later Outcomes for the Offspring?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and later outcomes for the child.

Primary Literature

As noted above in the introduction of this chapter, examination of later outcomes relied heavily on three cohorts, with some limited results from other hand-searched studies reported below.

The first of these cohorts was the Ottawa Prenatal Prospective Study (OPPS) by Fried and colleagues (Fried et al., 1998). The sample of 698 pregnant women was a convenience sample obtained through advertising in doctors' offices and in the media. It could be characterized as including low-risk middle-class women of European descent. No gestational criterion was used, but most of the women were in their second trimester of pregnancy. Data collection was by interview about drug use while pregnant, including the use of cigarettes, alcohol, and cannabis, the last of which was characterized in terms of the number of joints per week. Of the original 698 study participants, 140 women reported at least some use of cannabis or drinking at least 0.85 oz. of absolute alcohol per day or smoking at least 16 mg of nicotine per day (Fried et al., 1998). A smaller group of women ($n = 50$) who did not use any substances during pregnancy were randomly selected as a reference group. Among these women, prenatal maternal cannabis use was categorized into three groups, with levels averaged across pregnancy: (1) no use, (2) mild/moderate use up to six joints per week, and (3) heavy use of at least six joints per week. Offspring were followed until the ages 18 to 22 years, with some attrition as would be expected (Fried et al., 1998).

The second study, started in 1982, was the Maternal Health Practices and Child Development (MHPCD) Study (Day and Richardson, 1991). The sample was recruited from a single inner-city outpatient prenatal clinic in Pittsburgh and thus was of mixed race/ethnicity and lower socioeconomic status. The participants had to be at least 18 years of age and in their fourth month of pregnancy. Of the 1,360 participants who met these criteria and were screened by an interview, pregnant women who used two or more joints per month were then selected for the study, with a random sample of an equal number of women chosen from the remaining non-using subjects, for a total sample of 564 (Huizink, 2014). Prenatal cannabis use was expressed as average daily joints for each trimester of pregnancy separately, although there was some overlap. Follow-up data on offspring have been reported up to the age of 14.

The most recent study was the Generation R study started in 2001, a multiethnic (Dutch, Moroccan, Surinamese, and Turkish) population-based prospective cohort study from fetal life until adulthood in the city of Rotterdam, the Netherlands (Jaddoe et al., 2012). The sample consists of 9,778 mothers with a delivery date between April 2002 and January 2006, and the members of the sample tended to be of higher socioeconomic status (Huizink, 2014). All participating women in Generation R

filled out questionnaires on their substance use at three points in pregnancy corresponding to the three trimesters. In this sample, 220 women reported using cannabis in pregnancy, generally in the first trimester (Huizink, 2014). The study discriminated between cannabis exposure, tobacco smoking, and the use of neither. Data on the resulting children up to age 6 were used in this report.

Sudden Infant Death Syndrome

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and sudden infant death syndrome (SIDS).

Primary Literature Only one study was identified that examined the association between cannabis use and SIDS. In a case-control study of 428 infants who died of SIDS in southern California between 1989 and 1992, Klonoff-Cohen and Lam-Kruglic (2001) found no association between SIDS and cannabis exposure at conception (aOR, 1.1; 95% CI = 0.6–2.0; $p = 0.82$), during pregnancy (aOR, 0.6; 95% CI = 0.3–1.6; $p = 0.33$), or postnatally (aOR, 0.6; 95% CI = 0.2–1.8; $p = 0.42$). An interesting finding is increased risk of SIDS with paternal cannabis use at conception (aOR, 2.2; 95% CI = 1.2–4.2; $p = 0.01$), during pregnancy (aOR, 2.0; 95% CI = 1.0–4.1; $p = 0.05$), and postnatally (aOR, 2.8; 95% CI = 1.1–7.3; $p = 0.04$).

Breastfeeding

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and breastfeeding.

Primary Literature One narrative review (Garry et al., 2009) identified two early studies on the effects of cannabinoids in breast milk on subsequent motor function but found no consistency in the results. The authors noted the difficulty in studying this issue since prenatal exposure is also likely among other confounders of cannabis use. The committee's search identified one study of physical growth (Fried et al., 2001) which makes mention of no difference being found in choice and duration of breastfeeding relative to marijuana use.

Physical Growth

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and physical growth in the child.

Primary Literature Postnatal growth results were obtained from the OPPS (Fried et al., 2001). Growth was measured for 152 participants at 1 year, 2–4 years, 6 years, 12 years, and 13–16 years. There was a dose–response relationship between head circumference and cannabis exposure (measured as heavy or six or more joints per week, moderate or between zero and six joints per week, and none), with children of heavy cannabis users having the smallest head circumferences (Z-score, 0.84; SD = 1.3; $p = 0.08$), a finding that persisted through age 12 but was not seen at ages 13–16 (Fried et al., 2001). In addition, infants of heavy cannabis users were the lightest at birth (Z-score, 0.32; SD = 0.9), but they experienced substantial weight gain such that they were the heaviest at 1 year. Furthermore, at ages 13–16 no differences were seen in height, weight, ponderal index, or onset of puberty.

Cognition/Academic Achievement

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and cognition and academic achievement of the child.

Primary Literature The committee reviewed this literature in terms of preschool cognitive development and later cognitive development. Among the studies that examined cognitive development up to 3 years of age, no difference was found. In addition, two studies (OPPS and MHPCD) looked at cognitive development at 36–60 months. Both studies reported a weak effect on short-term memory.

Six studies out of two cohorts were identified that addressed the association between cannabis and cognitive function between ages 5 and 16 years using a variety of assessment instruments (Bluhm et al., 2006; El Marroun et al., 2010; Fried and Watkinson, 1988, 1990; Goldschmidt et al., 2012; Richardson et al., 1995). No differences in overall cognitive scores were found, but differences with exposure to different levels of prenatal cannabis were seen for some subscale scores, although they were not replicated across studies. In their assessment of school achievement, Goldschmidt et al. (2012) found worse reading scores at age 14 as measured by the Wechsler Individual Achievement Test (WIAT Screener). The

authors found a WIAT Screener basic reading score of 93.8 among non-exposed children, 93.1 among children exposed to less than one joint per day, and 87.8 among children exposed to one or more joints per day ($p = 0.001$).⁴ No differences with cannabis exposure were seen for cognitive or motor development in Fried and Watkinson (1988), Richardson et al. (1995), or El Marroun et al. (2010).

Behavior

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and later child behavior.

Primary Literature The committee sought studies linking prenatal marijuana exposure to later child behavior. Of the three cohorts assessed above, only one report dealt with child behavior problems (Bluhm et al., 2006). The remaining reports assessed behavior in testing situations: for example, variability in reaction times and errors on continuous performance tests. Because the committee felt the latter do not really capture the construct of interest, this section reports only on child behavior problems at age 18 months and 3 years. At 18 months, higher aggression scores were seen in girls but not in boys; this effect did not persist at 3 years (El Marroun et al., 2010).

Substance Use and Delinquency

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and later substance use and delinquency of the child.

Primary Literature The committee identified five reports from two cohorts (OPPS and MHPCD) that addressed the association between prenatal cannabis exposure and substance use and delinquency among offspring between 14 and 22 years of age. In the study addressing delinquency at age 14 years, prenatal cannabis exposure was found to be correlated with an increased risk of delinquent behavior (OR, 1.84; 95% CI = 1.05–2.96) (Day et al., 2015). However, this effect was mediated by depression and attention difficulties at age 10. Three studies addressed prenatal exposure to cannabis on the use of both cigarettes and cannabis in offspring ages 14 to 22 years. In Porath and Fried (2005), prenatal marijuana exposure more

⁴ This can be accounted for by attention and depression at age 10.

than doubled the risk of the initiation of cigarette smoking (OR, 2.58; 95% CI = 1.11–6.00) and daily cigarette smoking (OR, 2.36; 95% CI = 1.00–5.57). The authors also found that prenatal cannabis exposure also increased the risk of initiation of cannabis use in youth (OR, 2.76; 95% CI = 1.11–6.86) and increased the risk of using marijuana regularly (OR, 0.79; 95% CI = 0.33–1.90). Sonon et al. (2015) found that prenatal cannabis exposure was a predictor of offspring marijuana use (OR, 1.22; 95% CI = 1.02–1.44) at age 22 (Sonon et al., 2015).

Mental Health and Psychosis

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis exposure and later mental health and psychosis in the child.

Primary Literature At age 10, children in the MHPCD study with prenatal cannabis exposure in the first and third trimesters had worse scores on a measure of depressive symptoms. Using the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort study Zammit et al. (2009) found no difference in definite psychotic-like symptoms (PLIKS) as measured by a PLIKS semi-structured interview at 12 years of age between those exposed prenatally and those not exposed (aOR for linear trend, 0.91; 95% CI = 0.49–1.71; $p = 0.776$). Day et al. (2015), working with the MHPCD cohort at age 22, found that prenatal marijuana exposure was associated with an increased risk of psychotic symptoms as measured by the Diagnostic Interview Schedule (incidence density ratio [IDR] 1.31; $p < 0.05$). In a mediation model, considering the effect of early initiation use of cannabis, the youth risk was essentially the same (IDR, 1.27; $p = 0.06$).

Discussion of Findings

The literature reviewed above does not support an effect of cannabis exposure on overall cognitive function, although some variation in subscale scores has been seen. Only one study has examined overall child behavior, and it found that the results did not persist. More consistency is seen for adolescent outcomes, with increased delinquency, greater cigarette and cannabis use, and some suggestion of increased mental health symptoms. For the later outcomes, attributing the outcomes to prenatal exposures is particularly difficult. While the studies attempted to control for the child's environment using standard measures of socioeconomic status as well as a direct assessment of the home environment, these

approaches may be insufficient to detect potentially subtle differences in the family and neighborhood environments of women who smoke cannabis during pregnancy and those who do not. For example, the association of prenatal cannabis exposure and adolescent substance use may reflect family/neighborhood influences and may not be a direct effect of the prenatal exposure. Likewise, maternal distress/depression during pregnancy, which is likely to continue postpartum, may influence both the use of cannabis and child developmental outcomes. In addition, these studies did not address heritable or epigenetic vulnerability.

CONCLUSION 10-4 There is insufficient evidence to support or refute a statistical association between maternal cannabis smoking and later outcomes in the offspring (e.g., sudden infant death syndrome, cognition/academic achievement, and later substance use).

RESEARCH GAPS

To address the research gaps relevant to prenatal, perinatal, and neonatal outcomes, the committee suggests the following:

- There is a need for systematic inquiry using standardized questions about dose and duration at specific intervals in pregnancy to ascertain the level of prenatal cannabis exposure.
- Capitalizing, where possible, on the increase in toxicological screening at delivery to validate self-report measures.
- With the increased availability of recreational cannabis, observational studies need to be carried out—where ethical—on cannabis use and potential physiologic changes (e.g., blood pressure, etc.).
- Pooling, if possible, to obtain cohorts of women exposed only to THC and not to other drugs.
- A systematic follow-up of children exposed to cannabis prenatally with agreed-upon protocols and tests, with an ascertainment of the home and neighborhood environment regarding concurrent substance use.
- Developing strategies for assessing the effect of cannabis on pregnant women and fetuses through registries or systematic use of administrative data.

SUMMARY

This chapter summarizes the literature on prenatal, perinatal, and neonatal exposure to cannabis that has been published since 1999 and deemed to be of good or fair quality by the committee. Overall, there is substantial evidence of a statistical association between cannabis smoke and lower birth weight, but there is only limited, insufficient, or no evidence in support of any other health endpoint related to prenatal, perinatal, or neonatal outcomes. This may be due to a number of limitations faced by many of the research studies reviewed in this chapter, including an almost exclusive reliance on self-reporting to ascertain cannabis exposure, as is true in many areas of this report. While many studies used standardized questions regarding frequency and duration of cannabis use, others relied on data extracted from the medical record. Also, as with other portions of this report, the potency of cannabis varied across time. The lack of biological validation of self-reporting suggests caution is warranted. Moreover, dosage and timing of exposure in pregnancy is particularly important, as exposures early in pregnancy may affect organogenesis leading to birth defects, whereas later exposures are more likely to affect the growth of the fetus.

Second, even within substantial cohorts, the number of women who used cannabis exclusively was small. These sample sizes may have limited statistical power to detect many outcomes.

Third, cannabis exposure was almost exclusively through smoking and was often confounded by the use of other substances—namely, tobacco and alcohol. Although many authors relied on a variety of statistical techniques to isolate the effects of cannabis exposure, attribution of outcomes to cannabis alone was difficult. Even when cannabis is the sole exposure, it is not straightforward to attribute outcomes to THC alone versus the mode of exposure.

Finally, caution needs to be used in interpreting the numerous findings of “no association” in this chapter. Absent a pooled estimate of effect and confidence intervals, such conclusions may be based on a small number of studies, some of which may even conflict.

The committee has formed a number of research conclusions related to these health endpoints (see Box 10-1); however, it is important that each of these conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections.

BOX 10-1 Summary of Chapter Conclusions*

There is substantial evidence of a statistical association between maternal cannabis smoking and:

- Lower birth weight of the offspring (10-2)

There is limited evidence of a statistical association between maternal cannabis smoking and:

- Pregnancy complications for the mother (10-1)
- Admission of the infant to the neonatal intensive care unit (NICU) (10-3)

There is insufficient evidence to support or refute a statistical association between maternal cannabis smoking and:

- Later outcomes in the offspring (e.g., sudden infant death syndrome, cognition/academic achievement, and later substance use) (10-4)

* Numbers in parentheses correspond to chapter conclusion numbers.

REFERENCES

- Andrade, C. 2016. Cannabis and neuropsychiatry, 1: Benefits and risks. *Journal of Clinical Psychiatry* 77(5):551–554.
- Bailey, J. R., H. C. Cunney, M. G. Paule, and W. Slikker, Jr. 1987. Fetal disposition of delta 9-tetrahydrocannabinol (THC) during late pregnancy in the rhesus monkey. *Toxicology and Applied Pharmacology* 90(2):315–321.
- Berenson, A. B., G. S. Wilkinson, and L. A. Lopez. 1996. Effects of prenatal care on neonates born to drug-using women. *Substance Use and Misuse* 31(8):1063–1076.
- Bluhm, E. C., J. Daniels, B. H. Pollock, and A. F. Olshan. 2006. Maternal use of recreational drugs and neuroblastoma in offspring. *Cancer Causes and Control* 17(5):663–669.
- Budde, M. P., T. E. De Lange, G. A. Dekker, A. Chan, and A. M. T. Nguyen. 2007. Risk factors for placental abruption in a socio-economically disadvantaged region. *Journal of Maternal–Fetal and Neonatal Medicine* 20(9):687–693.
- CBHSQ (Center for Behavioral Health Statistics and Quality). 2016. 2015 National Survey on Drug Use and Health: Detailed tables. Rockville, MD: Substance Abuse and Mental Health Services Administration. <http://www.samhsa.gov/data/sites/default/files/NSDUH-DeT-Tabs2014/NSDUH-DeT-Tabs2014.pdf> (accessed November 23, 2016).
- CDPHE (Colorado Department of Public Health and Environment). 2015. *Monitoring health concerns related to marijuana in Colorado: 2014*. <http://www2.cde.state.co.us/artemis/hemonos/he1282m332015internet/he1282m332015internet01.pdf> (accessed November 23, 2016).

- Day, N. L., and G. A. Richardson. 1991. Prenatal marijuana use: Epidemiology, methodologic issues, and infant outcome. *Chemical Dependency and Pregnancy* 18(1):77–91.
- Day, N. L., L. Goldschmidt, R. Day, C. Larkby, and G. A. Richardson. 2015. Prenatal marijuana exposure, age of marijuana initiation, and the development of psychotic symptoms in young adults. *Psychological Medicine* 45(8):1779–1787.
- Dekker, G. A., S. Y. Lee, R. A. North, L. M. McCowan, N. A. Simpson, and C. T. Roberts. 2012. Risk factors for preterm birth in an international prospective cohort of nulliparous women. *PLOS ONE* 7(7):e39154.
- El Marroun, H., H. Tiemeier, E. A. P. Steegers, J. W. Roos-Hesselink, V. W. V. Jaddoe, A. Hofman, F. C. Verhulst, W. van den Brink, and A. C. Huizink. 2010. A prospective study on intrauterine cannabis exposure and fetal blood flow. *Early Human Development* 86(4):231–236.
- Fergusson, D. M., L. J. Horwood, and K. Northstone. 2002. Maternal use of cannabis and pregnancy outcome. *British Journal of Obstetrics and Gynaecology* 109(1):21–27.
- Forray, A., B. Merry, H. Lin, J. P. Ruger, and K. A. Yonkers. 2015. Perinatal substance use: A prospective evaluation of abstinence and relapse. *Drug and Alcohol Dependence* 150: 147–155.
- Forrester, M., and R. Merz. 2006. Comparison of trends in gastroschisis and prenatal illicit drug use rates. *Journal of Toxicology and Environmental Health, Part A: Current Issues* 69(13):1253–1259.
- Frank, D. A., H. Bauchner, S. Parker, A. M. Huber, K.-A. Kwabena, H. Cabral, and B. Zuckerman. 1990. Neonatal body proportionality and body composition after in utero exposure to cocaine and marijuana. *Journal of Pediatrics* 117(4):622–626.
- Fried, P. A., and B. Watkinson. 1988. 12- and 23-month neurobehavioural follow-up of children prenatally exposed to marihuana, cigarettes and alcohol. *Neurotoxicology and Teratology* 10:305–313.
- Fried, P. A., and B. Watkinson. 1990. 36- and 48-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol. *Developmental and Behavioral Pediatrics* 11(2):49–58.
- Fried, P. A., B. Watkinson, and R. Gray. 1998. Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana. *Neurotoxicology and Teratology* 20(3):293–306.
- Fried, P. A., D. S. James, and B. Watkinson. 2001. Growth and pubertal milestones during adolescence in offspring prenatally exposed to cigarettes and marihuana. *Neurotoxicology & Teratology* 23(5):431–436.
- Fryers, T., and T. Brugha. 2013. Childhood determinants of adult psychiatric disorder. *Clinical Practice and Epidemiology in Mental Health* 9:1–50.
- Garry, A., V. Rigourd, A. Amirouche, V. Faurox, S. Aubry, and R. Serreau. 2009. Cannabis and breastfeeding. *Journal of Toxicology* 2009(596149):1–5.
- Goldschmidt, L., G. A. Richardson, J. A. Willford, S. G. Severtson, and N. L. Day. 2012. School achievement in 14-year-old youths prenatally exposed to marijuana. *Neurotoxicology & Teratology* 34(1):161–167.
- Gray, T. R., R. D. Eiden, K. E. Leonard, G. J. Connors, S. Shisler, and M. A. Huestis. 2010. Identifying prenatal cannabis exposure and effects of concurrent tobacco exposure on neonatal growth. *Clinical Chemistry* 56(9):1442–1450.
- Gunn, J. K. L., C. B. Rosales, K. E. Center, A. Nunez, S. J. Gibson, C. Christ, and J. E. Ehiri. 2016. Prenatal exposure to cannabis and maternal and child health outcomes: A systematic review and meta-analysis. *BMJ Open* 6(4):e009986.
- Hashibe, M., K. Straif, D. P. Tashkin, H. Morgenstern, S. Greenland, and Z. Zhang. 2005. Epidemiologic review of marijuana use and cancer risk. *Alcohol* 35:265–275.

- Huang, Y. J., Z. Zhang, D. P. Tashkin, B. Fend, K. Straif, and M. Hashibe. 2015. An epidemiologic review of marijuana and cancer: An update. *Cancer Epidemiology, Biomarkers, and Prevention* 24(1):15–31.
- Huizink, A. 2014. Prenatal cannabis exposure and infant outcomes: Overview of studies. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 52:45–52.
- IOM (Institute of Medicine). 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC: National Academy Press.
- Irner, T. B. 2012. Substance exposure in utero and developmental consequences in adolescence: A systematic review. *Child Neuropsychology* 18(6):521–549.
- Jaddoe, V. W. V., C. M. van Duijn, O. H. Franco, A. K. van der Heijden, M. H. van IJzendoorn, J. C. de Jongste, A. van der Lugt, J. P. Mackenbach, H. A. Moll, H. Raat, F. Rivadeneira, E. A. P. Steegers, H. Tiemier, A. G. Uitterlinder, F. C. Verhulst, and A. Hofman. 2012. The Generation R study: Design and cohort update 2012. *European Journal of Epidemiology* 27(9):739–756.
- Janisse, J. J., B. A. Bailey, J. Ager, and R. J. Sokol. 2014. Alcohol, tobacco, cocaine, and marijuana use: Relative contributions to preterm delivery and fetal growth restriction. *Substance Abuse* 35(1):60–67.
- Klonoff-Cohen, H., and P. Lam-Kruglic. 2001. Maternal and paternal recreational drug use and sudden infant death syndrome. *Pediatrics and Adolescent Medicine* 155(7):765–770.
- Leemaqz, S. Y., G. A. Dekker, L. M. McCowan, L. C. Kenny, J. E. Myers, N. A. Simpson, L. Poston, and C. T. Roberts. 2016. Maternal marijuana use has independent effects on risk for spontaneous preterm birth but not other common late pregnancy complications. *Reproductive Toxicology* 62:77–86.
- Lubman, D., A. Cheetham, and M. Yucel. 2014. Cannabis and adolescent brain development. *Pharmacology and Therapeutics* (148):1–16.
- Metz, T. D., and E. H. Stickrath. 2015. Marijuana use in pregnancy and lactation: A review of the evidence. *American Journal of Obstetrics & Gynecology* 213(6):761–778.
- Porath, A. J., and P. A. Fried. 2005. Effects of prenatal cigarette and marijuana exposure on drug use among offspring. *Neurotoxicology & Teratology* 27(2):267–277.
- Richardson, G. A., N. L. Day, and L. Goldschmidt. 1995. Prenatal alcohol, marijuana, and tobacco use: Infant mental and motor development. *Neurotoxicology and Teratology* 17(4):479–487.
- Savitz, D. A., and P. Murnane. 2010. Behavioral influences on preterm birth: A review. *Epidemiology* 21(3):291–299.
- Schempf, A. H. 2007. Illicit drug use and neonatal outcomes: A critical review. *Obstetrical & Gynecological Survey* 62(11):749–757.
- Schempf, A. H., and D. M. Strobino. 2008. Illicit drug use and adverse birth outcomes: Is it drugs or context? *Journal of Urban Health* 85(6):858–873.
- Sonon, K. E., G. A. Richardson, J. R. Cornelius, K. H. Kim, and N. L. Day. 2015. Prenatal marijuana exposure predicts marijuana use in young adulthood. *Neurotoxicology and Teratology* 47:10–15.
- van Gelder, M. M., A. R. Donders, O. Devine, N. Roeleveld, J. Reefhuis, and the National Birth Defects Prevention Study. 2014. Using Bayesian models to assess the effects of under-reporting of cannabis use on the association with birth defects, National Birth Defects Prevention Study, 1997–2005. *Paediatric and Perinatal Epidemiology* 28(5):424–433.
- Varnier, M. W., R. M. Silver, C. J. Rowland Hogue, M. Willinger, C. B. Parker, V. R. Thorsten, R. L. Goldenberg, G. R. Saade, D. J. Dudley, D. Coustan, B. Stoll, R. Bukowski, M. A. Koch, D. Conway, H. Pinar, U. M. Reddy, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development Stillbirth Collaborative Research Network. 2014. Association between stillbirth and illicit drug use and smoking during pregnancy. *Obstetrics & Gynecology* 123(1):113–125.

- Viteri, O. A., E. E. Soto, R. O. Bahado-Singh, C. W. Christensen, S. P. Chauhan, and B. M. Sibai. 2015. Fetal anomalies and long-term effects associated with substance abuse in pregnancy: A literature review. *American Journal of Perinatology* 32(5):405–415.
- Warshak, C. R., J. Regan, B. Moore, K. Magner, S. Kritzer, and J. Van Hook. 2015. Association between marijuana use and adverse obstetrical and neonatal outcomes. *Journal of Perinatology* 35(12):991–995.
- Williams, J. H., and L. Ross. 2007. Consequences of prenatal toxin exposure for mental health in children and adolescents: A systematic review. *European Child & Adolescent Psychiatry* 16(4):243–253.
- Williams, L. J., A. Correa, and S. Rasmussen. 2004. Maternal lifestyle factors and risk for ventricular septal defects. *Birth Defects Research* 70(2):59–64.
- Witter, F. R. and J.R. Niebyl. 1990. Marijuana use in pregnancy and pregnancy outcome. *American Journal of Perinatology* 7(1):36–38.
- Wu, T. C., D. P. Tashkin, B. Djahed, and J. E. Rose. 1988. Pulmonary hazards of smoking marijuana as compared with tobacco. *New England Journal of Medicine* 318(6):347–351.
- Zammit, S., K. Thomas, A. Thompson, J. Horwood, P. Menezes, D. Gunnell, C. Hollis, D. Wolke, G. Lewis, and G. Harrison. 2009. Maternal tobacco, cannabis and alcohol use during pregnancy and risk of adolescent psychotic symptoms in offspring. *British Journal of Psychiatry* 195(4):294–300.

Psychosocial

Chapter Highlights

- Recent cannabis use impairs the performance in cognitive domains of learning, memory, and attention. Recent use may be defined as cannabis use within 24 hours of evaluation.
- A limited number of studies suggest that there are impairments in cognitive domains of learning, memory, and attention in individuals who have stopped smoking cannabis.
- Cannabis use during adolescence is related to impairments in subsequent academic achievement and education, employment and income, and social relationships and social roles.

Adolescence and emerging adulthood are the periods where most youths begin to experiment with substances of abuse, including cannabis (Johnston et al., 2015). Exploration for many substances of abuse have maintained historical consistency for the past few decades, with approximately 24.9 percent of youths having used cannabis at least one time by eighth grade to 51.4 percent having tried cannabis by the time they graduate from high school (Johnston et al., 2015). Yet, recent changes in recreational cannabis use laws have been linked to adolescents' changing perception around accessibility and availability of cannabis and decreased risk of harm from cannabis use, two factors that have been historically connected with rising rates of substance use (Feldstein Ewing et al., 2017;

Schmidt et al., 2016). The result is that we are at the forefront of a changing cannabis landscape for adolescents and young adults.

This is relevant because it is during this precise period of adolescence and young adulthood that the neural substrates that underlie the development of cognition are most active. Indeed, adolescence marks one of the most impressive stretches of neural and behavioral change (Giedd, 2015), with substantial and protracted development in terms of both brain structure and function throughout the teenage years and into the late 20s and early 30s (e.g., Conrod and Nikolaou, 2016). As a result, cannabis and other substance use during this period may incur relatively greater interference in neural, social, and academic functioning as compared to later developmental periods (e.g., adulthood) (Brumback et al., 2016; Jacobus et al., 2015).

However, with the paucity of data on the impact of changes of cannabis policy, coupled with existing limitations in the field of addiction neurodevelopment (e.g., predominance of cross-sectional studies) (Feldstein Ewing et al., 2014), we are still very much at the forefront of beginning to understand how cannabis impacts adolescent through adult cognitive health and broader psychosocial functioning.

COGNITION

Despite what appears, on first glance, to be a very broad existing literature, a surprisingly small number of empirical studies have examined how cannabis impacts the psychosocial domains targeted here. The questions addressed in this section revolve around how cannabis affects three aspects of cognition—memory, learning, and attention—areas that have continued to be prevalent across the self-report, neuropsychological, and magnetic resonance imaging (MRI)/functional magnetic resonance imaging (fMRI) literature since the mid-1970s. Furthermore, these are aspects of cognition that are often explored in other studies. In other words, evaluation of these aspects of cognition increases the potential to compare these findings to other studies, including the 10-year prospective examination of 10,000 youths across 21 sites (the ABCD study; Adolescent Brain Cognitive Development Study, 2016). In terms of the relevance of these aspects of cognition, the domains of learning, memory, and attention are central, as they undergird an individual's success—or failure—across such areas as academic, employment, and social/relationship functioning. This subsequently renders these three domains of cognition strong proxies for examining interference in functioning, one of the key metrics of cannabis use disorder symptomology according to *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V).

These domains are defined broadly in order to be as inclusive as pos-

sible of how they were measured within the included systematic analyses and component primary manuscripts, and to allow maximal potential for generalization to the broader literature. Thus, within this review, “memory” is defined as the wide array of function that involves the abilities to remember, temporarily store, more extensively store, process, manipulate, recall, and reproduce data (e.g., verbal, auditory, written). In this review, “learning” is defined as the wide array of function that involves the ability to observe, comprehend, absorb, and appropriate new information into an individual’s cognitive repertoire (e.g., verbal, auditory, visual). Finally, in this review, “attention” is defined as an individual’s ability to stay focused on the task at hand without being distracted but also to be cognitively flexible enough to transfer to a different task or set of information when the time requires (e.g., including brain regions relevant to visual, auditory, and verbal processing as well as executive control).

To investigate how cannabis affects these three domains of human cognition (memory, learning, attention), a search was conducted to identify systematic reviews of the existing published literature since the publication of *Marijuana and Medicine: Assessing the Science Base*, the last Institute of Medicine (IOM) report on marijuana (1999). There were a total of 94 systematic reviews identified that responded to the topic of cannabis and cognition during the period of 2000–2016. Of these, 5 systematic reviews were considered of good quality (Batalla et al., 2013; Broyd et al., 2016; Grant et al., 2003; Martin-Santos et al., 2010; Schreiner and Dunn, 2012). No primary manuscripts were utilized in this section because all study questions were addressed by the systematic reviews.

In contrast to other sections of this report, given the diversity of the metrics and constructs in learning, memory, and attention, and the different coverage of these domains within the 5 different systematic reviews, we present summaries from each of the systematic reviews in these domains rather than only presenting one representative systematic review for the topic area of cognition. Furthermore, reflective of the field of cognition at this time, the presented systematic reviews reflect data from the fields of neuropsychology, computer-administered cognitive tests, as well as brain structure and function (e.g., MRI/fMRI). The latter represent some of our most contemporary, sensitive, and specific metrics of cognitive function at this time.

It should be noted that Chapter 12 (Mental Health) highlights the multidirectional and complex relationship between cannabis use and cannabis use disorder and cognitive performance among individuals with psychotic disorders. For further information on this topic, please refer to Chapter 12.

The collection of systematic reviews used in this chapter represents a large body of work. The Broyd et al. (2016) systematic review is the most

recent, evaluating 3,021 total manuscripts, yielding a final number of 105 manuscripts in their review. Within their systematic review, they evaluated cannabis's interference with cognition across a number of assessment methodologies. Furthermore, they evaluated the impact of these cognitive domains across developmental periods, including adolescence, emerging adulthood, and adulthood (for additional information about developmental implications among adolescents, see Box 11-1). Batalla and colleagues began with 142 studies, which they narrowed to 43 manuscripts. As with the Broyd et al. (2016) team, Batalla et al. (2013) included studies

BOX 11-1 Developmental Implications Among Adolescents

While adolescents were clustered in many of these systematic reviews (e.g., Broyd et al., 2016), it is important to note that they were the minority, often less than 20 percent of the full sample, and rarely examined independently (e.g., Batalla et al., 2013) to uncover potential developmental differences in cognitive function and/or its interference between the age groups. Much work needs to be done specifically examining the impact of cannabis on these cognitive contexts in adolescents and emerging adults specifically (i.e., ages 14–25). This is highly important for three reasons. First, data in the cited systematic reviews and elsewhere (e.g., Batalla et al., 2013, and Filbey et al., 2015) continue to indicate that an early age of initiation tends to be connected to bigger differences in brain function during adulthood. Second, the brain does not complete development until approximately age 25 (e.g., Giedd, 2015), and data from the field of alcohol use reflect that substance use exposure during this period when the brain undergoes rapid transformation could have a more lasting impact on cognitive performance (e.g., Lisdahl et al., 2013). This interference in cognitive function during the adolescent and emerging adult years, which overlap with the critical period in which many youths' and young adults' primary responsibility is to be receiving their education, could very well interfere with these individuals' ability to optimally perform in school and other educational settings.

While the evidence for an association between cannabis use and effects on cognitive development during adolescence is limited at this time, the committee recognizes the important initiative recently begun by the National Institutes of Health (NIH) for the landmark study on brain development and child health, Adolescent Brain Cognitive Development (ABCD) Study (Adolescent Brain Cognitive Development Study, 2016). The ABCD study is the largest long-term study on cognitive development, tracking the biological and behavioral development of at least 10,000 children beginning at ages 9 to 10 for 10 years through adolescence into adulthood using neuropsychological evaluations and advanced brain imaging to observe brain growth with precision. This study, which began in 2015, will examine how biology and environment interact and relate to developmental outcomes such as physical health, mental health, and life achievements.

across the age span, including adolescents and adults. One of the older systematic reviews, Grant et al. (2003), commenced their review with 1,830 manuscripts, which were reduced to a group of 117 papers in their final evaluation. Martin-Santos et al. (2010) began their examination with 66 manuscripts, which resulted in a final set of 41 studies of cannabis's effect on cognition. Schreiner and Dunn (2012) started with more than 800 studies, which they narrowed to a final set of 13 studies.

In these systematic reviews, "acute" generally reflects cognitive domains assessed within a short window (often within several hours) immediately after cannabis use. The individual may or may not still be intoxicated during this examination. In contrast, "sustained" generally reflects cognitive domains assessed after a period of abstinence from cannabis. Within the reviewed studies, that ranges from several hours to months after discontinuing cannabis use.

Is There an Association Between Cannabis Use and Learning?

Systematic Reviews

Of our final set of five systematic reviews, three addressed cannabis use on the cognitive domain of learning (Broyd et al., 2016; Grant et al., 2003; Schreiner and Dunn, 2012).

In terms of acute impact of cannabis use on learning, primarily relying on word list learning, data from 11 manuscripts within the Broyd et al. (2016) systematic review contributed to "strong" support of acute cannabis use on interference in learning. However, in terms of sustained effects, Broyd et al. (2016) only showed "mixed" support. Grant et al. (2003) assessed sustained impact of cannabis use on learning via neuropsychological tests (e.g., California Verbal Learning Test–Learning Trials; Rey Auditory Verbal Learning Test–Learning Trial). Across nine component studies, Grant et al. (2003) found a small negative effect size (ES) of -0.21 (99% confidence interval [CI] = -0.39 to -0.022) for the sustained impact of cannabis on learning. Schreiner and Dunn (2012) also examined sustained impact on learning, with component studies also relying on neuropsychological metrics (e.g., California Verbal Learning Test–Learning Trials; Rey Auditory Verbal Learning Test–Learning Trials; VIG–Visual Learning). Using the criteria of cannabis abstinence for at least 1 month (measured as ≥ 25 days) within their 13 examined studies, they found a very small ES of -0.16 (95% CI = -0.33 – 0.02).

One example study of the component studies within this section includes a study by Hanson et al. (2010). In this study, 19 adolescent marijuana users (mean age = 18 years) with limited other alcohol and/or other substance use were compared with 21 demographically similar

non-using controls (mean age = 17.4 years). Participants completed neuropsychological batteries assessing learning and other cognitive domains at several points post-cessation (e.g., 3 days; 2 weeks; 3 weeks). Abstinence was verified via decreasing tetrahydrocannabinol metabolite values assessed via serial urine drug screens. Marijuana users showed initial poorer performance on learning as compared with non-using controls in acute assessments (at 3 days; $p < 0.01$). However, they showed significant improvements with cessation, with no differences observed on learning between the cannabis-using and non-cannabis-using groups at either of the sustained time points (e.g., 2 weeks; 3 weeks).

Primary Literature

In this review of cannabis, the primary literature was searched when the systematic review content did not fully cover or address study questions. Given the breadth and scope of the existing systematic reviews in this domain, additional primary literature was not searched for the domain of learning.

Is There an Association Between Cannabis Use and Memory?

Systematic Reviews

Of the final set of five systematic reviews, three addressed cannabis use on the cognitive domain of memory (Batalla et al., 2013; Broyd et al., 2016; Martin-Santos et al., 2010).

In terms of acute impact of cannabis use on memory, the Broyd et al. (2016) systematic review was the only one to address this question. In this review, 22 studies assessed memory, including working memory and other memory function using various neuropsychological tests such as the Sternberg task, Trails B, *n*-back, and Wechsler tests, including spatial working memory, digit span, and digit recall. These studies showed moderate to strong evidence for acute interference of cannabis on memory. In terms of a long-term sustained relationship between cannabis use and learning following abstinence, the 11 studies examined by Broyd et al. (2016) showed mixed to no evidence for interference in memory functioning after cessation from cannabis use. Similarly, Batalla et al. (2013) examined memory using seven MRI/fMRI studies. The range in mean days of abstinence in these studies extended from 7 days to 201 days post-cannabis cessation. Batalla et al. (2013) found that although there was no difference in task performance between cannabis users and cannabis nonusers, cannabis users engaged slightly different parts of their brains as compared to nonusers to accomplish the task, often described in

the neuroimaging literature as the utilization of “compensatory” efforts. Similar to Batalla et al. (2013), Martin-Santos et al. (2010) examined five empirical MRI/fMRI studies. Individuals in these studies had abstained from using cannabis for an average of 24 hours to 26 days. As with Batalla et al. (2013), cannabis users showed equivalent performance across the neuroimaging tasks to the nonusers, but they could have engaged in compensatory efforts to achieve these outcomes.

One example study in the memory systematic analyses includes a recent study by Roten and colleagues (2015). This is a pharmacotherapy trial of 78 youth ages 15 to 21 years seeking treatment for cannabis dependence. These youths were evaluated to ensure their abstinence from cannabis use via urine cannabinoid testing. They received a computer-administered battery of tests, including verbal memory, visual memory, and composite memory. Youths who were recently abstinent and continuously abstinent for 4 weeks showed significantly better memory performance as compared to youths who were still using cannabis at the 4 week measurement (difference [d] = 7.2 ± 2.1 , $p < 0.001$ and $d = 7.5 \pm 2.4$, $p = 0.002$, respectively).

Primary Literature

In this review of cannabis, the primary literature was searched when the systematic review content did not fully cover or address study questions. Given the breadth and scope of the existing systematic reviews in this domain, additional primary literature was not searched for the domain of memory.

Is There an Association Between Cannabis Use and Attention?

Systematic Reviews

Of our final set of five systematic reviews, four addressed cannabis use on the cognitive domain of attention (Batalla et al., 2013; Broyd et al., 2016; Grant et al., 2003; Schreiner and Dunn, 2012).

To determine the acute impact of cannabis use on attention, Broyd et al. (2016) reviewed 17 studies that assessed attention using several approaches, including using neuropsychological metrics of continuous task performance, divided attention tasks, reaction time, and attention control tasks. The synthesized findings from studies showed strong evidence for acute interference of cannabis on attention, as reported by the authors.

In terms of the long-term sustained relationship between cannabis use and attention following abstinence, 10 studies examined by Broyd et

al. (2016) showed mixed evidence for impairment in attention functioning after cessation from cannabis use. Likewise, using a series of MRI and fMRI measures (e.g., attention network task, functional connectivity via Multi-Source Interference Task) with three studies, Batalla et al. (2013) showed limited evidence of differences in task performance, but as with the other domains, they found evidence that cannabis users may be engaging a different neural network to achieve similar outcomes during the task (e.g., compensatory efforts). In a review of 11 studies, Grant et al. (2003) also examined the long-term sustained relationship between cannabis use and attention following abstinence. In their study, Grant et al. (2003) examined attention primarily using neuropsychological measures, finding a small ES for the influence of cannabis use on attention (ES, -0.083 ; 99% CI = -0.32 – 0.15). Finally, Schreiner and Dunn (2012) primarily examined neuropsychological test performance to determine any sustained impact of cannabis on attention performance, including the Continuous Performance Task and the Iowa Gambling Task (IGT). With the 13 component studies, the authors found a small ES for the sustained impact of cannabis on attention (ES, -0.20 ; 95% CI = -0.49 – 0.09).

An example of a component study from this section includes Crane et al. (2013). This study included 69 cannabis using 18- to 24-year-olds (mean age = 21 years). Attention was measured with four neuropsychological measures, including the IGT, the Balloon Analogue Risk Task, the Monetary Choice Questionnaire, and the GoStop Task. Interestingly, cannabis use was only associated with a significant difference on one measure (IGT and past year cannabis use, $p < 0.03$; IGT and past-month cannabis use, $p < 0.003$). There were no significant sustained associations between cannabis use on the other three measures of inhibition (for past year cannabis use and past-month cannabis use for the Balloon Analogue Risk Task, the Monetary Choice Questionnaire, and the GoStop Task).

Primary Literature

In this review of cannabis, the primary literature was searched when the systematic review content did not fully cover or address study questions. Given the breadth and scope of the existing systematic reviews in this domain, additional primary literature was not searched for the domain of attention.

Discussion of Findings

In sum, within the domain of learning, the Broyd et al. (2016) systematic review and the component study highlighted within that review showed strong data for the acute (immediate) impact of cannabis use on

learning. However, results from three systematic reviews (Batalla et al., 2013; Broyd et al., 2016; Martin-Santos et al., 2010) reflected limited to no support for the association between the sustained effects of cannabis use after cessation and the cognitive domain of learning. Similarly, for the domain of memory, the Broyd et al. (2016) systematic review and the component study within it showed moderate to strong evidence for the acute (immediate) impact of cannabis use on memory. However, as with learning, there were limited to no data to support the association between the sustained effects of cannabis use after cessation and the cognitive domain of memory in the three systematic reviews that addressed this question (Batalla et al., 2013; Broyd et al., 2016; Martin-Santos et al., 2010). Of interest, the neuroimaging studies reflected that while there was no difference in terms of performance on memory tasks, cannabis users may recruit different parts of their brain to achieve equivalent performance to control subjects on these tasks, suggesting the need to examine how cannabis may impact the neural regions that drive the processing of memory in future research. Finally, for the domain of attention, the Broyd et al. (2016) systematic review showed strong evidence for the acute (immediate) impact of cannabis on attention. However, as with the other domains, the evidence from other systematic reviews (Batalla et al., 2013; Broyd et al., 2016; Grant et al., 2003; Martin-Santos et al., 2010; Schreiner and Dunn, 2012) suggest that there were limited to no data to support the association between the sustained effects of cannabis use after cessation and the cognitive domain of attention.

CONCLUSION 11-1

- 11-1(a) There is moderate evidence of a statistical association between acute cannabis use and impairment in the cognitive domains of learning, memory, and attention.**
- 11-1(b) There is limited evidence of a statistical association between sustained abstinence from cannabis use and impairments in the cognitive domains of learning, memory, and attention.**

ACADEMIC ACHIEVEMENT

Is There an Association Between Cannabis Use and Academic Achievement and Education?

For the psychosocial areas that go beyond cognition, there was one systematic review (Macleod et al., 2004) that examined the effects of can-

nabis on a number of psychosocial outcomes as reported in longitudinal studies of general population samples. Specifically, this review contributed to our evaluation of the research literature related to the effects of cannabis on academic achievement as well as social relationships and other social roles. There was no systematic review of the research literature on the effects of cannabis on employment and income.

Because only one systematic review was available, we also focused on the primary literature to address questions related to the effect of cannabis on (1) academic achievement; (2) employment and income; and (3) social relationships and other social roles. The primary literature to be reviewed and summarized is based on studies published subsequent to 1999. In selecting that literature, we focused on studies that met criteria derived from the Newcastle–Ottawa quality assessment scale. In particular, (1) prospective studies in which cannabis use occurred prior to the outcomes of interest; (2) multiple assessments of the variables of interest over time; (3) samples that are representative, either of the nation or a major subgroup; (4) multiple measures of cannabis use, involving frequency and/or quantity of use; (5) a relatively large sample size; and (6) consideration of relevant sociodemographic control variables such as sex/gender, age, family income, ethnicity/race, and/or history related to the outcome of interest.

Systematic Reviews

In their systematic review, Macleod et al. (2004) identified 16 high-quality longitudinal studies of the general population in which the effects of cannabis use on psychosocial outcomes, including educational attainment, were examined. The authors reported that cannabis use was consistently related to negative educational outcomes (measured primarily by drop-out rates), but they also noted that the strength of the association varied across the studies reviewed. In addition, including the appropriate control variables in the analyses typically resulted in a substantial decrease in the strength of the association. There was no evidence of a causal relationship between cannabis use and lower educational attainment.

Primary Literature

The primary literature published subsequent to Macleod et al.'s 2004 review continues to show that it is difficult to document a direct link between cannabis use and negative educational outcomes because other variables play a role. At best, indirect relationships have been reported. For example, Arria et al. (2013) used longitudinal growth curve modeling to analyze cannabis use and grade point average (GPA) data across 4

years of university education. They found no direct links from cannabis to GPA, but they did report an indirect path in which increased cannabis use led to increased skipping of classes, which resulted in lower GPA. Using data from the Coronary Artery Risk Development in Young Adults study, Braun et al. (2000) initially found an inverse relationship between past-month cannabis use and becoming a college graduate. When analyses were adjusted for variables such as age and parental education, this relationship disappeared, so that cannabis use was unrelated to college graduation.

There is some evidence to suggest that a higher frequency and persistence of cannabis use are associated with some negative educational outcomes. Using data from the Victoria Adolescent Health Cohort (1992–2003), Degenhardt et al. (2010) examined a cohort of a representative sample of Australian students ($n = 1,943$) from an average age of 14.9 years through an average of 24.1 years. Individuals who were persistent or weekly users of cannabis in adolescence and young adulthood had poorer post-school outcomes at age 24 years (adjusted odds ratio [aOR], 0.84; 95% CI = 0.55–1.3; $n = 190$)¹ compared with individuals who never used cannabis. Adjustment for background factors and cigarette smoking reduced this association.

The age at which cannabis use is initiated may be important in determining negative educational outcomes. Using data from three Australian cohort studies involving more than 6,000 participants, Horwood et al. (2010) reported that individuals who began to use cannabis before age 15 years experienced significantly greater negative educational outcomes, even after reductions in odds ratios (ORs) based on an adjustment for confounding variables. Pooled odds ratios (pOR) estimates indicated that the educational achievement of those who never used cannabis by age 18 years were 1.9 to 2.9 times greater than for those who used cannabis before the age of 15 years. The researchers found that individuals who had not used cannabis by age 18 were more likely to complete high school (pOR, 2.9; 95% CI = 1.8–4.6; $p < 0.001$), enroll in university (pOR, 1.9; 95% CI = 1.5–2.4; $p < 0.001$), and earn a university degree (pOR, 2.5; 95% CI = 1.8–3.5; $p < 0.001$) compared to individuals who had used cannabis before age 18. In related findings, Brook et al. (2002) reported that minority youths ages 10 to 19 years who used cannabis had higher rates of being suspended or expelled from school (aOR, 2.68; 95% CI = 1.73–4.14; $p < 0.001$).

Educational outcomes related to cannabis use tend to be confounded with the use of other substances, particularly tobacco/smoking cigarettes. Mokrysz et al. (2016) analyzed data from the Avon Longitudinal Study of

¹ Adjusted for non-Australian birth, symptoms of depression and anxiety in adolescence, high-risk alcohol use, and maximum level of cigarette smoking in adolescence.

Parents and Children, a prospective study of 2,235 adolescents, 24 percent of whom reported using cannabis by the age of 15 years. When analyses included appropriate confounding variables (particularly tobacco use) even heavy (≥ 50 times) cannabis users (mean educational performance,² 69.2 percent; 95% CI = 65.0–73.3) did not significantly differ from never users in their educational performance at age 16 (mean educational performance, 80.8 percent; 95% CI = 80.2–81.4).

Similarly, McCaffrey et al. (2010) followed 4,500 adolescents for 4 years through high school and reported a positive association between cannabis use and dropout rates (OR, 5.6; risk ratio [RR] = 3.8). However, the remaining association (OR, 2.4; RR = 1.7) became statistically insignificant when the data were adjusted for cigarette use. Degenhardt et al.'s 2010 study found that occasional cannabis use was linked to lower educational outcomes (i.e., dropping out of school), but that the initial relationship was attenuated by tobacco use, which was relatively high in their sample. Green and Ensminger (2006) found that heavy use of cannabis during adolescence was associated with dropping out of school.

Discussion of Findings

Researchers have hypothesized and some studies have reported that cannabis use is linked to negative educational outcomes. However, the relationships among these variables are complex as are the ways in which the specific variables of interest are measured. In addition, all such research requires the careful consideration of a wide range of control variables that include sociodemographic confounders (e.g., gender/sex, family socioeconomic status [SES]) and educational confounds (e.g., parental education, intelligence quotient [IQ], student's cognitive ability) (Fergusson and Boden, 2008; Horwood et al., 2010). This complexity requires that researchers use sophisticated data-analytic techniques (e.g., propensity scoring to reduce confounding by measured factors) (McCaffrey et al., 2010). Use of less sophisticated approaches (e.g., correlations, logistic regression) can lead to an overestimation of the association between cannabis use and negative educational outcomes (McCaffrey et al., 2010). Typically, the primary literature cannot elucidate the mechanisms through which cannabis use may produce negative educational outcomes, although some have speculated that these outcomes may be related to cannabis's effects on the brain, including cognitive impairment.

In all of the primary research literature reviewed on the effects of cannabis on academic achievement, employment and income, as well as social relationships and other social roles, there were a number of

² Measured in percentage of General Certificate of Secondary Education points.

limitations. Below, we summarize aspects of various studies that make it difficult to draw definitive conclusions regarding the causal relationships among cannabis use and the different psychosocial outcomes that we examined. They include the following:

1. Sample heterogeneity (e.g., differences related to sample's SES, age, gender, ethnicity).
2. Inconsistent measures of cannabis use (yes/no; cross-sectional reports of frequency and/or quantity/amount; categories based on history of use).
3. Inconsistent/varying measures of the duration of cannabis use and outcome variables.
4. Even in longitudinal studies, the measures of interest often are cross-sectional snapshots.
5. The history and persistence of cannabis use is not always considered. In adolescence through adulthood, patterns of cannabis use can vary (groupings include consistent never users, occasional users, persistent heavy users, and so on).
6. In almost every study, the measure of cannabis use is based only on self-report, which cannot be validated.
7. Failure to consider individual characteristics (e.g., attitudes related to the outcomes of interest).
8. Multiple substances being used; it is difficult to separate out effects of cannabis relative to use of other drugs, including alcohol and smoking tobacco. Often cannabis effects are less strongly related to outcomes of interest.
9. The complexity of the relationships means that confounds must be considered and statistical analyses must be sophisticated. Many studies meet criteria for design and samples, but report outcomes based on less sophisticated analyses (e.g., correlations, logistic regressions).

CONCLUSION 11-2 There is limited evidence of a statistical association between cannabis use and impaired academic achievement and education outcomes.

EMPLOYMENT AND INCOME

Is There an Association Between Cannabis Use and Employment and Income?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and employment and income.

Primary Literature

The primary literature to be reviewed and summarized is based on studies published subsequent to 1999. In selecting that literature, the committee focused on studies that met criteria derived from the Newcastle-Ottawa criteria (Wells et al., 2014), as described in the previous section.

Popovici and French (2014) analyzed two waves of panel data from the nationally representative National Epidemiologic Survey on Alcohol and Related Conditions. Initial analyses suggested a significant association between cannabis and employment status (implying poorer labor market outcomes; also see Fergusson and Boden, 2008). However, more sophisticated (fixed-effect) data analyses that considered individual sources of heterogeneity resulted in smaller and less significant relationships between cannabis and unemployment for men and women (OR, 0.813; 95% CI = 0.237–2.791 and OR, 0.777, 95% CI = 0.269–2.239, respectively). The researchers concluded that cannabis use is less detrimental to labor market participation than was suggested in previous research. A similar conclusion was reached by Lee et al. (2015a), who found that cannabis use was not related to unemployment (OR, 0.96; 95% CI = 0.91–1.01), but rather that it is confounded with the use of other substances such as drinking alcohol and tobacco use, which are associated with unemployment.

There are some studies that suggest that the persistent use of cannabis over longer periods of time is associated with unemployment. Zhang et al. (2016) reported that chronic cannabis users (who started in adolescence) were more likely to be unemployed at age 43 (across three decades) than non/experimental users (aOR, 3.51; 95% CI = 1.13–10.91). Braun et al. (2000) also found cannabis users to be less likely to be employed than nonusers. Those who were employed tended to have lower prestige occupations (measured by the Occupational Prestige Score [OPS]; across 10 years) compared to nonusers. Some of this may be related to lessened commitment to work among those who use cannabis over time. Hyggen (2012) found low work commitment (as measured by the Work Involvement

ment Scale) among cannabis users compared to abstainers, starting from young adulthood (ages 17 to 20 years) through to middle age (early to mid-40s).

Some of the negative effects of cannabis use on unemployment may be exacerbated among those from low SES backgrounds (Lee et al., 2015a). Other studies of low SES and minority samples also report that chronic cannabis use is related to increased unemployment (Green and Ensminger, 2006; Lee et al., 2015b). Disentangling the effects of cannabis use from other variables related to having a low SES and/or a disadvantaged background may be fruitful areas for future research.

Discussion of Findings

All of the committee's conclusions are based on primary literature. In some cases, especially with more sophisticated data analyses, cannabis use has not been linked to outcomes such as labor market participation and unemployment. In other cases, a longer duration of cannabis use has been associated with unemployment. A lower SES may exacerbate these negative outcomes. Along with the limitations described on page 280, our examination of the literature on the relationship between cannabis use and employment was limited by the difficulty in determining causality. Because employment status is not static, it is possible that the relationships may be cyclical (e.g., depending on context, unemployment could contribute to the use of cannabis and other substances [Lee et al., 2015a] and cannabis/substance use could contribute to unemployment).

CONCLUSION 11-3 There is limited evidence of a statistical association between cannabis use and increased rates of unemployment and/or low income.

SOCIAL RELATIONSHIPS AND OTHER SOCIAL ROLES

Is There an Association Between Cannabis Use and Social Functioning and Social Roles?

Systematic Reviews

There was one systematic review that examined the effects of cannabis on social functioning as one of a number of outcomes in longitudinal studies of general population samples. In their systematic review, Macleod et al. (2004) identified 16 high-quality longitudinal studies of the general population in which the effects of cannabis use on psychosocial outcomes, including social functioning, were examined. The authors found that can-

nabis use was inconsistently related to social functioning as manifested by antisocial behaviors such as conduct disorder or delinquency, offending, and contact with police. Associations related to an individual's gender and ethnicity also produced inconsistent findings. Using data from the Christchurch Health and Development Study ($n = 1,265$), Fergusson et al. (1996) reported that cannabis use at younger ages (<15 years) was consistently associated with antisocial behavior (aOR, 1.0; 95% CI = 0.5–2.1). Interestingly, the use of tobacco and alcohol showed similar associations.

Primary Literature

The primary literature has shown that there is a statistical association between cannabis use and social functioning as manifested by negative relationships with others, but there are too few good-quality studies to provide conclusive evidence of causation. Palamar et al. (2014) examined various psychosocial outcomes in a nationally representative sample of high school seniors ($n = 7,437$) from the Monitoring the Future study. They found that participants who had used cannabis 40 or more times had compromised relationships with teachers, supervisors, and parents. Cannabis users reported less interest in activities and more trouble with police. Interestingly, the adverse psychosocial outcomes for cannabis were less than those for alcohol. In a sample of African American and Puerto Rican young adults, cannabis use was associated with rebelliousness and engagement with fewer productive activities (Brook et al., 2002).

Chassin et al. (2010) reported that in a sample of juvenile offenders, cannabis use in adolescence was inversely related to “psychosocial maturity” (i.e., a measure of responsibility, temperance, and perspective taking) in young adulthood ($\chi^2(5) = 13.49$, $p = 0.02$; comparative fit index [CFI] = 0.991, RMSEA = 0.038). Such maturity is integral to being able to successfully engage in social relationships and to transition into adult social roles. Interestingly, in some cases the temporal sequencing of cannabis use and maturity fluctuated over time, suggesting that these relationships were not static; increases in cannabis use were associated with reduced maturity, and reductions in cannabis use were associated with increases in maturity.

There is some evidence to suggest that a higher frequency and persistence of cannabis use or, in particular, cannabis use during adolescence is associated with some negative social outcomes. Among a low-income sample of 274 African Americans, Green and Ensminger (2006) found that “heavy” (>20 times) cannabis use during adolescence (i.e., before age 17 years) was associated with poorer functioning in some social roles at ages 32 to 33 years. Compared to never using or experimenting with cannabis, heavy cannabis use was associated with unemployment (ES, -0.159 ; 95%

CI = -0.303 to -0.155 ; $p = 0.030$) and to parenting outside of marriage (ES, 0.109 ; 95% CI = -0.042 – 0.261).

Discussion of Findings

In the systematic review and primary literature, the findings indicate inconsistent relationships between cannabis use and social functioning. The primary literature included studies in which there was a relationship between cannabis use and adverse outcomes such as compromised relationships with authority figures and poorer functioning in social roles such as employment and parenting. Various limitations faced by the primary literature are described on page 282.

Researchers have hypothesized—and some studies have reported—that cannabis use is linked to negative social functioning and the ability to appropriately handle social roles. The relationships among these variables are complex, as are the ways in which the specific variables of interest are measured. In addition, all such research requires the careful consideration of a wide range of control variables that include sociodemographic confounds (e.g., gender/sex, family SES), the use of other substances (alcohol, other illicit drugs), and psychological problems such as depression or a personality disorder (Macleod et al., 2004). This complexity requires that researchers use sophisticated data-analytic techniques (e.g., propensity scoring to reduce selection bias; see Chassin et al., 2010). The use of less sophisticated approaches (e.g., correlations, logistic regression) can lead to an overestimation of the association between cannabis use and negative social outcomes (Macleod et al., 2004).

CONCLUSION 11-4 There is limited evidence of a statistical association between cannabis use and impaired social functioning or engagement in developmentally appropriate social roles.

RESEARCH GAPS

To address the research gaps relevant to cognitive health and psychosocial functioning, the committee suggests the following:

- The systematic reviews that were reviewed by the committee did not necessarily parallel those in other fields of research that are covered in this report. As such, more studies that report quantitative data on the psychosocial effects of cannabis use are required to allow for a greater degree of comparison with the effects of cannabis use on the other health endpoints discussed in this report.

BOX 11-2

Special Consideration for Psychosocial Systematic Reviews

The quality assessment of the systematic reviews in this chapter followed the methods used in this report. Most of the systematic reviews focused on the literature on cognition (i.e., learning, memory, attention) as related to behavioral, neuropsychological, and neuroimaging findings (Batalla et al., 2013; Broyd et al., 2016; Grant et al., 2003; Martin-Santos et al., 2010; Schreiner and Dunn, 2012). There was only one systematic review (Macleod et al., 2004) that included outcomes related to academic achievement/education and social functioning/social roles. In the systematic reviews on cognition, it is important to note that the broad reporting standards for the field of behavioral, neuropsychological, and neuroimaging findings included limitations related to the failure to consistently describe the methods for scoring the evidence for each endpoint. For example, within this examination of the literature, many systematic reviews followed the standards typically used to evaluate findings from the primary literature. That is, the reviews include scores of the strength and consistency of the evidence for each outcome, but they provided less information about issues such as study design and statistical analyses. As a result, the reviews did not include the conventions generally found within quantitatively based systematic examinations of a topic, or such as would be found in meta-analytic reviews (e.g., empirical demarcations of synergy or dissonance, as reported via effect sizes and confidence intervals). Reasons for this may include variations in study methodologies, instrumentation, populations, and research designs, which may be relatively more prevalent within psychosocial research. Other reasons may reflect the relatively small body of literature that meets the quality criteria for inclusion in the systematic review. For example, Broyd et al. (2016) evaluated 3,021 manuscripts that yielded a final sample of only 105 manuscripts that addressed the cognitive outcomes of interest. The state-of-the-science in such research often includes confounds that make it difficult to identify effects that unequivocally can be linked to cannabis. Thus, research designed to examine the impact of cannabis on the developing brain often has to contend with confounds related to polysubstance use (which is characteristic of adolescent cannabis use), which obscures the ability to answer questions about the effects of “cannabis only” on the developing brain and cognitive functioning. In some cases, samples included different populations (adolescents versus adults), cannabis use history (i.e., chronic versus acute), and patterns of use (i.e., frequency, dose, quantity), all of which provide mixed or inconsistent evidence as to the effects of cannabis on a specific outcome. In their systematic review, Macleod et al. (2004) noted that when analyses were appropriately adjusted to address such confounds, there was a substantial decrease in the strength of associations between cannabis use and negative educational outcomes. Similar conclusions can be reached when examining the literature in a broad range of topics. All of these issues provide the basis for recommendations regarding future research on psychosocial outcomes. The findings from such research will begin to provide the evidence base for future systematic reviews and meta-analyses that can better articulate the effects of cannabis on behavior and functioning.

- It will be necessary to conduct further research on the developmental implications of cannabis use across age groups, particularly among adolescents, children, and the older populations. While the National Institute on Drug Abuse's Adolescent Brain Cognitive Development study is in progress (see Box 11-2), at the time that this report was released, the findings of that study had not been published.

SUMMARY

This chapter summarizes the good- and fair-quality psychosocial literature published since 1999. The committee found that there is moderate evidence of an association between cannabis use and the impairment of the cognitive domains of verbal learning and attention but insufficient evidence for an association between cannabis use and the impairment of working memory. There is mixed evidence for the persistence of impairments or the recovery of function following an abstinence period of 24 hours or several weeks (25–32 days) without cannabis use in the domains of working memory, attention, and verbal learning (Broyd et al., 2016).

The committee found that it is difficult to document a direct link between cannabis use and negative educational outcomes because other variables play a role. There is some evidence to suggest that a higher frequency and persistence of cannabis use is associated with some negative educational outcomes. The age at which cannabis use is initiated may be important in determining negative educational outcomes. Educational outcomes related to cannabis use tend to be confounded with the use of other substances, particularly tobacco/smoking cigarettes. The primary literature has shown that there is an association between cannabis use and social functioning as manifested by negative relationships with others, but there are too few good-quality studies to provide conclusive evidence. There is some evidence to suggest that a higher frequency and persistence of cannabis use or cannabis use during adolescence is associated with some negative social outcomes. The literature provides limited evidence to support the hypothesis that cannabis use contributes to negative social functioning (e.g., conduct disorder, immature behavior) or to a failure to engage in developmentally appropriate social roles (e.g., marriage, parenting). The committee has formed a number of research conclusions related to these health endpoints (see Box 11-3); however, it is important that each of these conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections.

BOX 11-3 Summary of Chapter Conclusions*

There is moderate evidence of a statistical association between cannabis use and:

- The impairment in the cognitive domains of learning, memory, and attention (acute cannabis use) (11-1a)

There is limited evidence of a statistical association between cannabis use and:

- Impaired academic achievement and education outcomes (11-2)
- Increased rates of unemployment and/or low income (11-3)
- Impaired social functioning or engagement in developmentally appropriate social roles (11-4)

There is limited evidence of a statistical association between *sustained abstinence from cannabis use* and:

- Impairments in the cognitive domains of learning, memory, and attention (11-1b)

* Numbers in parenthesis correspond to chapter conclusion numbers.

REFERENCES

- Adolescent Brain Cognitive Development Study. 2016. *Adolescent Brain Cognitive Development Study (ABCD)*. <http://abcdstudy.org> (accessed October 11, 2016).
- Arria, A. M., L. M. Garnier-Dykstra, E. T. Cook, K. M. Caldeira, K. B. Vincent, R. A. Baron, and K. E. O'Grady. 2013. Drug use patterns in young adulthood and post-college employment. *Drug and Alcohol Dependence* 127(1):23–30.
- Batalla, A., S. Bhattacharyya, M. Yucel, P. Fusar-Poli, J. A. Crippa, S. Nogue, M. Torrens, J. Pujol, M. Farre, and R. Martin-Santos. 2013. Structural and functional imaging studies in chronic cannabis users: A systematic review of adolescent and adult findings. *PLOS ONE* 8(2):e55821.
- Braun, B. L., P. Hannan, M. Wolfson, R. Jones-Webb, and S. Sidney. 2000. Occupational attainment, smoking, alcohol intake, and marijuana use: Ethnic-gender differences in the CARDIA study. *Addictive Behaviors* 25(3):399–414.
- Brook, J. S., R. E. Adams, E. B. Balka, and E. Johnson. 2002. Early adolescent marijuana use: Risks for the transition to young adulthood. *Psychological Medicine* 32(1):79–91.
- Broyd, S. J., H. H. Van Hell, C. Beale, M. Yucel, and N. Solowij. 2016. Acute and chronic effects of cannabinoids on human cognition—A systematic review. *Biological Psychiatry* 79(7):557–567.

- Brumback, T., N. Castro, J. Jacobus, and S. Tapert. 2016. Effects of marijuana use on brain structure and function: neuroimaging findings from a neurodevelopmental perspective. *International Review of Neurobiology* 129:33–65.
- Chassin, L., J. Dmitrieva, K. Modecki, L. Steinberg, E. Cauffman, A. R. Piquero, G. P. Knight, and S. H. Losoya. 2010. Does adolescent alcohol and marijuana use predict suppressed growth in psychosocial maturity among male juvenile offenders? *Psychology of Addictive Behaviors* 24(1):48–60.
- Conrod, P. K., and K. Nikolaou. 2016. Annual research review: On the developmental neuropsychology of substance use disorders. *Journal of Child Psychology and Psychiatry* 57(3):371–394.
- Crane, N.A., R. M. Schuster, and R. Gonzalez. 2013. Preliminary evidence for a sex-specific relationship between amount of cannabis use and neurocognitive performance in young adult cannabis users. *Journal of the International Neuropsychological Society* 19:1009–1015.
- Degenhardt, L., C. Coffey, J. B. Carlin, W. Swift, E. Moore, and G. C. Patton. 2010. Outcomes of occasional cannabis use in adolescence: 10-year follow-up study in Victoria, Australia. *The British Journal of Psychiatry* 196(4):290–295.
- Feldstein Ewing, S.W., S. J. Blakemore, and A. Sakhardande. 2014. The effect of alcohol consumption on the adolescent brain: A systematic review of MRI and fMRI studies of alcohol-using youth. *NeuroImage: Clinical* 5:420–437.
- Feldstein Ewing, S.W., T. I. Lovejoy, and E. Choo. 2017. How has legal recreational cannabis impacted adolescents in your state? A window of opportunity. *American Journal of Public Health* 107(2):246–247.
- Fergusson, D. M., and J. M. Boden. 2008. Cannabis use and later life outcomes. *Addiction* 103(6):969–976.
- Fergusson, D. M., M. T. Lynskey, and L. J. Horwood. 1996. The short-term consequences of early onset cannabis use. *Journal of Abnormal Child Psychology* 24:499–512.
- Filbey, F. M., T. McQueeney, S. Kadamangudi, C. Bice, and A. Ketcherside. 2015. Combined effects of marijuana and nicotine on memory performance and hippocampal volume. *Behavioural Brain Research* 293:46–53.
- Giedd, J. N. 2015. The amazing teen brain. *Scientific American* 312(6):32–37.
- Grant, I., R. Gonzalez, C. L. Carey, L. Natarajan, and T. Wolfson. 2003. Non-acute (residual) neurocognitive effects of cannabis use: A meta-analytic study. *Journal of the International Neuropsychological Society* 9:679–689.
- Green, K. M., and M. E. Ensminger. 2006. Adult social behavioral effects of heavy adolescent marijuana use among African Americans. *Developmental Psychology* 42(6):1168–1178.
- Hanson, K. L., J. L. Winward, A. D. Schweinsburg, K. L. Medina, S. A. Brown, and S. F. Tapert. 2010. Longitudinal study of cognition among adolescent marijuana users over three weeks of abstinence. *Addictive Behaviors* 35(11):970–976.
- Horwood, L. J., D. M. Fergusson, M. R. Hayatbakhsh, J. M. Najman, C. Coffey, G. C. Patton, E. Silins, and D. M. Hutchinson. 2010. Cannabis use and educational achievement: Findings from three Australasian cohort studies. *Drug and Alcohol Dependence* 110(3):247–253.
- Hyggen, C. 2012. Does smoking cannabis affect work commitment? *Addiction* 107(7):1309–1315.
- IOM (Institute of Medicine). 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC: National Academy Press.
- Jacobus, J., L. K. Squeglia, A. D. Meruelo, N. Castro, T. Brumback, J. N. Giedd, and S. F. Tapert. 2015. Cortical thickness in adolescent marijuana and alcohol users: A three-year prospective study from adolescence to young adulthood. *Developmental Cognitive Neuroscience* 16:101–109.

- Johnston, L. D., P. M. O'Malley, R. A. Miech, J. G. Bachman, and J. E. Schulenberg. 2015. *Monitoring the Future national survey results on drug use, 1975–2014. 2014 Overview: Key findings on adolescent drug use*. Ann Arbor: Institute for Social Research, the University of Michigan.
- Lee, J. O., K. G. Hill, L. A. Hartigan, J. M. Boden, K. Guttmanova, R. Kosterman, J. A. Bailey, and R. F. Catalano. 2015a. Unemployment and substance use problems among young adults: Does childhood low socioeconomic status exacerbate the effect? *Social Science and Medicine* 143:36–44.
- Lee, J. Y., J. S. Brook, S. J. Finch, and D. W. Brook. 2015b. Trajectories of marijuana use from adolescence to adulthood predicting unemployment in the mid 30s. *American Journal on Addictions* 24(5):452–459.
- Lisdahl, K. M., E. R. Wright, N. E. Wright, and S. Shollenbarger. 2013. Dare to delay? The impacts of adolescent alcohol and marijuana use onset on cognition, brain structure, and function. *Frontiers in Psychiatry* 4(53):1–19.
- Macleod, J., R. Oakes, A. Copello, I. Crome, M. Egger, M. Hickman, T. Oppenkowski, H. Stokes-Lampard, and G. Davey Smith. 2004. Psychological and social sequelae of cannabis and other illicit drug use by young people: A systematic review of longitudinal, general population studies. *Lancet* 363(9421):1579–1588.
- Martin-Santos, R., A. B. Fagundo, J. A. Crippa, Z. Atakan, S. Bhattacharyya, P. Allen, P. Fusar-Poli, S. Borgwardt, M. Seal, G. F. Busatto, and P. McGuire. 2010. Neuroimaging in cannabis use: A systematic review of the literature. *Psychological Medicine* 40(3):383–398.
- McCaffrey, D. F., R. L. Pacula, B. Han, and P. Ellickson. 2010. Marijuana use and high school dropout: The influence of unobservables. *Health Economics* 19(11):1281–1299.
- Mokrysz, C., R. Landy, S. H. Gage, M. R. Munafò, J. P. Roiser, and H. V. Curran. 2016. Are IQ and educational outcomes in teenagers related to their cannabis use? A prospective cohort study. *Journal of Psychopharmacology*. doi: 0269881115622241.
- Palamar, J. J., M. Fenstermaker, D. Kamboukos, D. C. Ompad, C. M. Cleland, and M. Weitzman. 2014. Adverse psychosocial outcomes associated with drug use among U.S. high school seniors: A comparison of alcohol and marijuana. *American Journal of Drug and Alcohol Abuse* 40(6):438–446.
- Popovici, I., and M. T. French. 2014. Cannabis use, employment, and income: Fixed-effects analysis of panel data. *Journal of Behavioral Health Services & Research* 41(2):185–202.
- Roten, A., N. L. Baker, and K. M. Gray. 2015. Cognitive performance in a placebo-controlled pharmacotherapy trial for youth with marijuana dependence. *Addictive Behaviors* 45:119–123.
- Schmidt, L. A., L. M. Jacobs, and J. Spetz. 2016. Young people's more permissive views about marijuana: Local impact of state laws or national trend? *American Journal of Public Health* 106(8):1498–1503.
- Schreiner, A. M., and M. E. Dunn. 2012. Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: A meta-analysis. *Experimental and Clinical Psychopharmacology* 20(5):420–429.
- Wells, G. A., B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, and P. Tugwell. 2014. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed November 24, 2016).
- Zhang, C., J. S. Brook, C. G. Leukefeld, and D. W. Brook. 2016. Trajectories of marijuana use from adolescence to adulthood as predictors of unemployment status in the early forties. *American Journal on Addictions* 25(3):203–209.

12

Mental Health

Chapter Highlights

- Cannabis use is likely to increase the risk of developing schizophrenia and other psychoses; the higher the use, the greater the risk.
- In individuals with schizophrenia and other psychoses, a history of cannabis use may be linked to better performance on learning and memory tasks.
- Cannabis use does not appear to increase the likelihood of developing depression, anxiety, and posttraumatic stress disorder.
- For individuals diagnosed with bipolar disorders, near daily cannabis use may be linked to greater symptoms of bipolar disorder than for nonusers.
- Heavy cannabis users are more likely to report thoughts of suicide than are nonusers.
- Regular cannabis use is likely to increase the risk for developing social anxiety disorder.

The relationship between substance use and mental health has been a long-standing and complex public health issue. In 2014, a national survey from the Substance Abuse and Mental Health Services Administration found that 20.2 million adults had a substance use disorder, and of these

individuals, 7.9 million had both a mental health disorder and a substance use disorder (SAMSHA, 2015). These statistics emphasize the importance of conducting cross-disciplinary research in order to appropriately inform public health decisions and ultimately improve population health. In this chapter, the committee reviews the current evidence on the association between cannabis use and prioritized mental health outcomes.

The mental health outcomes selected for review in this report were derived from the committee's statement of task and the sponsors' expressed interest and based on committee consensus. Specifically, mental health outcomes with high prevalence (e.g., depression and anxiety disorders) were included, as were outcomes with significant public health implications such as suicide. Studies on the association between cannabis use and schizophrenia and psychosis were included based on the large volume of literature on the subject, and in an effort to evaluate cannabis effects across the mental health diagnostic spectrum, studies on the association between cannabis use and bipolar disorder were reviewed as well.

Concerning each disorder, the committee focused on two key questions: What is the effect of cannabis use on the risk of developing the disorder? And in patients with the disorder, what are the effects of cannabis use on the symptoms or course of the disorder? An initial search of the primary literature (see Appendix B) produced a substantial number of primary articles (e.g., cross-sectional studies, case-control studies, cohort studies, randomized controlled trials [RCTs], or nonsystematic literature reviews) for the committee to review. Due to the time constraints of the study, additional search constraints were added to zero in on the types of studies that would likely produce the clearest research conclusions. For example, for the health endpoints discussed below, literature searches were limited to articles that included the following search terms: longitudinal, prospective, and case-control.¹ The committee's review of the literature focused on identifying studies relevant to answering these specific questions. In this chapter the committee will discuss the findings from 14 of the most recent, good- to fair-quality systematic reviews and from 31 primary literature articles that best address the committee's research questions of interest.

It is important to note that the present review does not include findings from controlled laboratory studies. These studies have been used to assess the effect of cannabis on behavior, to understand how cannabis interacts with alcohol and other drugs to influence behavior, and to characterize the dose-dependent effects of cannabis as they relate to its

¹ The initial search of the primary literature produced a relatively small literature base for the posttraumatic stress disorder section, and as such, the additional search restrictions were not applied.

potential for addiction. Evidence from this body of research—though illuminating at the mechanistic level—does not provide information on the mental health effects of cannabis use in real-world conditions, and was excluded for this reason.

SCHIZOPHRENIA AND OTHER PSYCHOSES

Schizophrenia spectrum disorders and other psychotic disorders are mental health disorders characterized by three different classes of symptoms: positive symptoms (e.g., delusions, hallucinations, or disorganized or abnormal motor behavior), negative symptoms (e.g., diminished emotional expression, lack of interest or motivation to engage in social settings, speech disturbance, or anhedonia), and impaired cognition (APA, 2013, p. 87; NIMH, 2015). Evidence suggests that the prevalence of cannabis use among people with schizophrenia is generally higher than among the general population (McLoughlin et al., 2014). In most of the studies reviewed below, schizophrenia, schizophreniform disorder, schizoaffective disorder, and psychotic disorders are used as aggregate endpoints. Therefore, conclusions regarding the association between cannabis use and psychosis are in general not diagnosis specific.

Is There an Association Between Cannabis Use and the Development of Schizophrenia or Other Psychoses?

Systematic Reviews

Five systematic reviews of fair or higher quality were identified that addressed the committee's research question (Large et al., 2011, Marconi et al., 2016, Moore et al., 2007, Myles et al., 2012, van der Meer et al., 2012). While the systematic review by Marconi et al. was the most recent, it excluded studies that did not consider at least three levels of cannabis exposure because the researchers' main purpose was to address dose-response relationships. In addition to reporting on the systematic review by Marconi et al., the systematic review conducted by Moore et al. is also discussed. This study addressed the broad question of cannabis use and psychotic outcome and included meta-analysis results. The remaining systematic reviews, which are not reported on here, focused on the time to onset of psychosis (or the age of onset of psychosis), the role of concomitant tobacco use, and psychotic symptomatology in patients at high risk of psychosis.

The systematic review by Marconi et al. (2016) included a search of the literature through December 31, 2013, and selected 10 studies for inclusion in the meta-analysis. A key feature of the researchers' inclusion criteria

was the requirement that studies assess cannabis use with a dose criterion and classify cannabis use into at least three exposure groups. Thus, high-quality studies with cannabis assessed as a dichotomous variable were excluded from the analysis. Studies that reported psychotic symptoms on a continuous, rather than categorical, scale were also excluded from the analysis. The 10 studies reviewed were conducted in Australia, Europe, New Zealand, and the United States and reported results for 66,816 individuals. The age and sex of the subjects were not reported. Cannabis use was classified based on lifetime frequency, the frequency of use at baseline, the duration/frequency of current use, and frequency within the last year. The authors did not assess the quality of the papers included in the meta-analysis, but they did conduct analyses to assess publication bias and heterogeneity. They considered the publication bias to be low and acknowledged the existence of heterogeneity within their sample of studies. Marconi et al., (2016) found an association between cannabis use and psychosis (odds ratio [OR], 3.9; 95% confidence interval [CI] = 2.84–5.34) among the most severe cannabis users, as compared to the nonusers. The investigators also report a dose–response relationship with an OR of 1.97 (95% CI = 1.68–2.31) for those at the median of any cannabis use and an OR of 3.40 (95% CI = 2.55–4.54) for those in the top 20 percent of cannabis use. In addition, they reported associations of cannabis use with the presence of psychotic symptoms (pooled odds ratio [pOR], 3.59; 95% CI = 2.42–5.32), as well as with a diagnosis of schizophrenia or psychotic disorder (pOR, 5.07; 95% CI = 3.62–7.09). Subgroup analysis stratified by study design revealed a pOR of 3.99 (95% CI = 2.50–6.37) for cross-sectional studies and 3.83 (95% CI = 2.34–6.29) for cohort studies.

Moore et al. (2007) searched multiple databases from their inception through September 2006 and included only studies that were longitudinal, population-based, or case-control studies nested within longitudinal designs. They assessed study quality by recording information on sampling strategy, response rates, missing data, attrition, attempts to address reverse causation, intoxication effects, and other potential confounders. Their search identified 32 studies, with 11 studies reporting the incidence of psychosis from 7 cohort studies, 5 of which were adult population-based cohorts and 2 of which were birth cohorts. They found no evidence of the presence of publication bias using Egger’s test ($p = 0.48$). The authors noted that some individual studies adjusted for psychotic symptoms at previous assessments or baseline and excluded people with psychotic symptoms or diagnosis at baseline to help clarify the temporal order of events. The authors also noted that individual studies excluded psychotic symptoms that arose solely from drug use by using scales to measure drug intoxication. In addition, this group of studies collectively adjusted for approximately 60 different potential confounders, including

other substance use, personality traits, sociodemographic markers, intellectual ability, and other mental health problems. In a pooled analysis, the authors found that in individuals who have ever used cannabis, there was an associated increased risk of a psychotic outcome (adjusted odds ratio [aOR], 1.41; 95% CI = 1.20–1.65). When the analysis was restricted to studies examining the effects of frequent cannabis use, the investigators found a stronger association (aOR, 2.09; 95% CI = 1.54–2.84), suggesting a dose–response relationship between cannabis use and the risk of a psychotic outcome.

Primary Literature

Auther et al. (2015) used the North American Prodrome Longitudinal Study² phase 1 sample to examine the impact of the level of cannabis use on conversion to psychosis.³ From the subjects who contributed to the data, 370 were determined to be at a high risk for developing a psychotic disorder. After excluding subjects who were missing necessary outcome data—or who met criteria for attenuated positive symptom syndrome, brief intermittent psychotic syndrome, genetic high risk, and deterioration syndrome—a total of 283 subjects (mean age = 18.3 years) were included in the study’s analysis. Using the subjects’ reported level of lifetime use, subjects were divided into three subgroups: no use, use without impairment, and abuse and dependence. The primary outcome, conversion to psychosis, was determined by meeting the full criteria for Presence of Psychotic Syndrome on the Structured Interview for Prodromal Syndrome. In a follow-up assessment (approximately 17 months after the initial baseline assessment), the researchers found that cannabis abuse/dependence was associated with a greater risk of conversion to psychosis within the chronic high-risk population; however, when alcohol use was incorporated into the Cox regression model, cannabis abuse/dependence was no longer significantly related to conversion (hazard ratio [HR], 1.875; 95% CI = 0.963–3.651). Similar research conclusions were reached in a longitudinal study by Valmaggia et al. (2014), where they examined the association between lifetime cannabis use and the development of psychosis. Valmaggia et al. (2014) followed 182 individuals at ultra-high risk for psychosis disorder for 2 years and found that varying degrees of cannabis use (i.e., frequent use, early-onset use, and continued use

² The North American Prodrome Longitudinal Study is a collaborative database formed in 2007. The database contains data on various clinical, cognitive, and functioning variables collected from eight independent research centers.

³ Auther et al. (2015) defined this outcome as having a psychotic level positive symptom that is either seriously disorganizing or dangerous, or that occurs for at least 1 hour per day for an average of 4 days in the past month.

after presentation) among lifetime cannabis users is associated with an increased transition to psychosis. It is of note, however, that within this specific ultra-high risk population, cannabis users were no more likely to develop psychosis than were those who had never tried cannabis.

Using a case-control design of 410 patients with first episode psychosis and 370 population controls, Di Forti et al. (2015) showed that first-episode psychosis patients were more likely to have lifetime cannabis use, more likely to use cannabis every day, and to mostly use high-potency cannabis as compared to the controls. The cases were also more likely to have used cannabis before the age of 15. Duration of use did not differ between patients and controls, nor did other drug use. After adjusting for a variety of confounders, including use of other drugs and alcohol, the researchers found an increased risk of developing psychosis in subjects who used cannabis daily (OR, 3.04; 95% CI = 1.91–7.76) and in subjects who used high-potency cannabis (OR, 2.91; 95% CI = 1.52–3.60). In a cross-sectional study of subjects with first-episode psychosis, Colizzi et al. (2015) examined the association between cannabis use, the risk of psychosis, and the dopamine receptor type 2 (DRD2) polymorphism rs1076560. Researchers found, after adjusting for confounders (e.g., gender, age, ethnicity, polysubstance use), a significant interaction between lifetime frequency of cannabis use and DRD2 polymorphism rs1076560 on psychosis risk. Moreover, a lifetime history of cannabis use was associated with an increased risk of having psychotic disorder in T-carrying subjects, relative to GG carrying subjects (OR, 3.07; 95% CI = 1.22–7.63).⁴

Discussion of Findings

The association between cannabis use and the development of a psychotic disorder is supported by data synthesized in several good-quality systematic reviews. The magnitude of this association is moderate to large and appears to be dose-dependent, and it may be moderated by genetic factors. Factors contributing to the strength of the evidence derived from the cited systematic reviews include large sample sizes, the relative homogeneity of the findings, the presence of relationships between the dose/exposure and the risk, the studies having been controlled for confounders, and the systematic reviews having assessed for publication bias. The primary literature reviewed by the committee confirms the conclusions of the systematic reviews, including the association between cannabis use

⁴ T-carrying subjects have at least one allele with the polymorphism. G-carrying subjects do not express the polymorphism. Genotype results of the subjects included homozygote G/G, heterozygote G/T, and homozygote T/T genotype classes. Due to the low number of TT subjects, GT and T/TT subjects were combined and compared to GG carriers.

and psychotic outcome and the dose-dependency of the effects, further bolstering the overall strength of evidence for our conclusions.

The limitations of the summarized studies include their reliance of self-report for cannabis use, issues with study designs (e.g., a lack of randomization), a lack of information on the frequency of use, patterns of long-term use, and possible confounding polysubstance effects. In addition, for the primary studies cited, some are also limited in terms of their sample sizes and controlling for confounders. Overall, the accumulated evidence is suggestive that cannabis use is associated with an increase in psychosis-related outcomes, as made evident in the discussion of Auther et al. (2015) and Valmaggia et al. (2014) above.

As noted in Box 12-1, the relationship between cannabis use and cannabis use disorder, and psychoses may be multidirectional and complex. The committee found this to be consistent with their review of the summarized data demonstrating a strong and consistent association between cannabis use and the subsequent development of psychosis and psychotic disorders. In addition, it is noteworthy to state that in certain societies, the incidence of schizophrenia has remained stable over the past 50 years despite the introduction of cannabis into those settings (Kirkbride et al., 2012); however, the committee did not examine ecologic data (studies of concomitant time trends) to evaluate trends in cannabis consumption and diagnosis of psychosis over time. Multiple factors (including measurement of dose and frequency of cannabis consumption over decades, and patterns of diagnosis of psychosis) limit our ability to draw conclusions from such findings. Of note, future analysis of rates of psychosis in states with increased access to cannabis could be tracked to provide valuable information regarding potential causal relationships between cannabis use and psychosis.

CONCLUSION 12-1 There is substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with the highest risk among the most frequent users.

BOX 12-1
Comorbidity in Substance Abuse and Mental Illness

National survey studies suggest that it is not uncommon for individuals with mental health disorders to use substances of abuse and, likewise, that it is not uncommon for individuals who abuse or are dependent on drug substances to also meet diagnostic criteria for a mental health disorder. In fact, in a 2014 national survey, almost 8 million adults in the United States reported co-occurring substance abuse and mental health disorders. This co-occurrence is also termed *comorbidity*.

There are a number of proposed explanations for why the comorbidity of substance abuse and mental health disorders exists. Three of the most commonly explored hypotheses are:

1. *Substance use may be a potential risk factor for developing mental health disorders.* Given the overlap in associated neurochemical substrates (e.g., dopamine, serotonin), specific neurobiological alterations due to drug use may have resulting effects on the neural processes regulating mental health.
2. *Mental illness may be a potential risk factor for developing a substance abuse disorder.* Research suggests that individuals who are at risk for a mental health disorder, or those who experience subclinical symptoms, may be more likely than others to use drugs as a form of self-medication.
3. *An overlap in predisposing risk factors (e.g., genetic vulnerability, environment) may contribute to the development of both substance abuse and a mental health disorder.* Studies suggest that the development of mental health disorders and substance abuse disorders may be a symptomatic outcome of preexisting neurobiological abnormalities (e.g., receptor abnormalities, epigenetic modifications).

Although the precise explanation is still unclear, it is reasonable to assume that comorbidity between substance abuse and mental health disorders may occur due to a mixture of proposed scenarios. With this context in mind, however, it is important to note that the issue of comorbidity directly affects the ability to determine causality and/or directionality in associations between substance use and mental health outcomes. This is a complex issue, one that certainly warrants further investigation.

SOURCES: CBHSQ, 2015; EMCDDA, 2016; NIDA, 2011.

Is There an Association Between Cannabis Use and the Course or Symptoms of Schizophrenia or Other Psychoses?

Systematic Reviews

Positive Symptoms One systematic review was identified that assessed the effects of cannabis use on positive symptoms⁵ in patients with psychotic disorders, but the researchers did not conduct a quantitative synthesis of the findings (Zammit et al., 2008). An additional systematic review (Szoke et al., 2014) addressed the effects of cannabis on schizotypal symptom dimensions; however, the committee will report only on the conclusions reported by Zammit et al. (2008) because they provide information about patients with psychotic disorders rather than schizotypy.

After their assessment of the literature, Zammit et al. (2008) found mixed evidence for the effects of cannabis use on positive symptoms in patients with psychotic disorders, with studies reporting statistically significant but small associations between cannabis use and the severity of positive symptoms. The authors searched multiple databases through November 2006, screened 15,303 references, and identified 13 cohort studies (n = 1,413) for their review. Studies were included if they were longitudinal or were case-control studies nested in longitudinal designs to assure that cannabis use was measured before outcome ascertainment. The authors excluded cohorts of individuals with dual diagnoses (psychosis and cannabis misuse or dependence) because of the limitations on comparisons to control groups. The authors assessed the quality of the studies by comparing the response rate at baseline, loss to follow-up, masking of outcome assessment, adjustment for baseline severity, adjustment for alcohol and other substances, and adjustment for confounders. Their quality assessment is reported in a summary table, and the authors noted that the most likely source of confounding would be the lack of adjustment for baseline severity and a lack of adjustment for alcohol and other substances in several of the studies. The authors did not report sample sizes, the age or sex of the study participants, or the definitions of cannabis use. The authors noted that several of the reviewed studies varied in their consideration of confounders, such as the use of other substances and baseline symptom severity, and that the lack of an association may be explained by a random misclassification of exposure data, particularly self-reports of cannabis use.

⁵ Positive symptoms of schizophrenia may include delusions, hallucinations, or abnormal motor behavior.

Negative Symptoms In the systematic review described above, Zammit et al. (2008) identified 4 studies (from the 13 cohort studies identified in the larger systematic review) that assessed the effects of cannabis use on negative symptoms⁶ in patients with psychotic disorders. Zammit et al. (2008) did not conduct a quantitative analysis of findings; in their review however, they found that cannabis use was not associated with negative symptom scores in three studies, but it was associated with reduced negative symptom scores in a fourth study. It should be noted that the fourth study did not control for confounders or baseline differences in symptoms.

Cognition Three systematic reviews were identified that assessed the relationship between cannabis abuse and dependence and cognition effects (e.g., disorganized thinking) in patients with psychotic disorders (Donoghue and Doody, 2012; Rabin et al., 2011; Yucel et al., 2012). A distinctive feature of this group of studies is the varying approaches to separating cannabis use from other substances. While the systematic review by Donoghue and Doody (2012) reported on all types of illegal substance abuse, it identified a subgroup of three studies focusing on cannabis use. This is in contrast to the work of Yucel and colleagues (2012) who included studies with patient groups who abused substances other than cannabis, and by Rabin et al. (2011), who considered cannabis use without other substance use but relied on cross-sectional studies only.

Donoghue and Doody (2012) conducted a search for relevant studies published between 1980 and October 2010, and from an initial pool of 7,075 studies, the authors selected 19 studies for further review. Three of the 19 studies focused on cannabis use. The three studies (n = 551) used the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria to define cannabis abuse or dependence, and DSM-IV criteria to define schizophrenia or schizoaffective disorders. All three studies included inpatients and outpatients, as well as patients with a dual diagnosis. In their review of these studies, the authors found that cannabis users performed better on various measures of cognition, including verbal learning and memory, attention and psychomotor, and global cognitive factor tests, than did non-cannabis users. The authors conducted a meta-analysis of the three studies and reported statistically significant associations between cannabis use and verbal learning and memory (Hedges $g^7 = 0.351$, 95% CI = 0.179–0.523), attention and psychomotor

⁶ Negative symptoms of schizophrenia may include diminished emotional expression, lack of interest or motivation to engage in social settings, speech disturbance, or anhedonia.

⁷ Hedges g reports the unbiased estimate of the effect size (the standardized difference between two means). It is commonly used for small sample sizes.

speed (Hedges $g = 0.316$, 95% CI = 0.144–0.488), and global cognitive factor (Hedges $g = 0.237$, 95% CI = 0.083–0.390). Tests of association with working memory and executive function were not statistically significant.

Rabin et al. (2011) conducted a meta-analysis on 8 cross-sectional studies, published between 2005 and 2010, with a total of 942 patients with schizophrenia. The 356 cannabis users among those patients had a mean age of 28.7 years, a mean education of 11.4 years, and 81.9 percent were male. Of the 942 patients, 586 were nonusers of cannabis and had a mean age of 32.4 years, a mean education of 12.2 years, and 65.8 percent were male. Limited information was provided about the statistical analysis, and the authors reported moderate associations with cannabis users performing better on general cognitive ability and intelligence; selective, sustained and divided attention; and visual-spatial and constructional abilities.

Yucel et al. (2012) searched the literature for the period between 1987 and March 2010 and included studies where cannabis was the predominant substance used by patients. They identified 10 studies involving 572 patients with schizophrenia; the studies were stratified by lifetime versus current or recent use. From their review, Yucel et al. (2012) found that patients with established schizophrenia and a history of cannabis use showed better performance on tests assessing cognitive abilities than did patients who did not use cannabis. For example, the meta-analysis conducted on 10 studies to assess global cognition resulted in a Cohen's d^8 of 0.35 (95% CI = 0.09–0.61; $p = 0.009$), showing small to moderate increases in performance in cannabis users compared to nonusers. Other small to moderate statistically significant effects were observed, again showing better performance by cannabis users compared to nonusers for processing speed, visual memory, and planning, despite the smaller number of studies available for these comparisons. The authors stated that tests for publication bias or heterogeneity were conducted, but these were only partially reported. No differences were reported for assessments of attention, verbal memory, or working memory.

Primary Literature

Positive Symptoms In a 2004 case-control study with schizophrenic patients, Rehman and Farooq (2007) determined that patients with cannabis abuse had higher rates of positive symptoms than nonusers. Seddon et al. (2016), in a case-control study examining cannabis use in the first year following a first-episode psychosis, found that cannabis use at baseline

⁸ Cohen's d is an estimate of the effect size (the standardized difference between two means).

or the 1-year assessment was associated with greater severity of positive symptoms (as measured by the Positive and Negative Syndrome Scale [PANSS], 2.14; 95% CI = 1.41–2.88) and a decrease in global functioning (as measured by the Global Assessment of Functioning symptom scale [–3.27; 95% CI = –6.04 to –0.49]). In contrast, Barrowclough et al. (2013) found no association between cannabis use and positive symptoms in patients with non-affective psychotic disorders, as assessed by PANSS (adjusted coefficient = 0.07; 95% CI = –0.21–0.34). Moreover, using a longitudinal analysis over 24 months, the researchers found that changes in cannabis dose did not predict changes in positive symptoms severity, even when patients became abstinent. In their study, the researchers conducted a cross sectional analysis of 160 patients with a clinical diagnosis of non-affective psychotic disorder and a DSM-IV diagnosis of drug and/or alcohol dependence or abuse. Notable strengths of this study are its dose–response analysis and its detailed quantification of cannabis use, with mean use in the sample being 4 days per week and an average of 2.4 grams per day. However, the results were not adjusted for confounders, including other drug use.

Another study, Dubertret et al. (2006) conducted a cross-sectional analysis on 205 patients with schizophrenia (n = 121 with no substance abuse; n = 38 cannabis users) and found that after controlling for other substance use, no association between cannabis use and positive symptoms was evident. A cross-sectional analysis by Tosato et al. (2013) (n = 311 patients) found no association between cannabis use and the severity of positive symptoms in a population of first-episode psychosis patients. Similarly, in a prospective, longitudinal cross-sectional study by Barrowclough et al. (2015), the authors found no specific association between cannabis dose and positive symptoms (n = 102; adjusted coefficient, 0.01; 95% CI = –0.24–0.25), and reductions in cannabis use during follow-up (longitudinal analysis up to 18 months) were not associated with improvements in positive PANSS symptoms in cannabis-using subjects after adjusting for confounders, including other drug use (n = 65; adjusted coefficient, –0.12; 95% CI = –0.45–0.22). After adjustment for confounders, abstinence from cannabis (90 days preceding the assessment) was found to be related to improved global functioning (adjusted coefficient, 4.95; 95% CI = 0.46–9.44). After controlling for confounders, van Dijk et al. (2012) found no difference between cannabis users (n = 68) and nonusers (n = 77) with schizophrenia with regard to the severity of baseline schizophrenia symptoms (p = 0.61; assessed by the Clinical Global Impression scale). The researchers also found no relationship between amount of cannabis used and the level of psychopathology (p = 0.676; as measured by PANSS).

Negative Symptoms Dubertret et al. (2006), using a cross-sectional analysis, found that after controlling for other drug substances, cannabis use was strongly associated with fewer negative symptoms of avolition—apathy ($p = 0.0001$)—as compared to non-cannabis users. Barrowclough et al. (2013), also using a cross-sectional analysis, found that previous 90-day cannabis use was not significantly associated with the severity of negative symptoms (adjusted coefficient, 0.12; 95% CI = -0.05 – 0.29). The longitudinal analysis of data from this cohort (up to 24 months) revealed no association between cannabis dose and negative symptom severity (adjusted coefficient, 0.18; 95% CI = -0.14 – 0.51). Similarly, a prospective longitudinal study by Barrowclough et al. (2015) found no association between cannabis dose and negative symptoms after adjustment for confounders, including other drug use (adjusted coefficient, 0.28; 95% CI = -0.04 – 0.61). Seddon et al. (2016) found that cannabis use at baseline or the 1-year assessment was not associated with differences in negative symptoms relative to nonusers (as measured by PANSS; -0.07 ; 95% CI = -1.11 – 0.97).

Cognition Power et al. (2015) found no association between lifetime cannabis use or cannabis dependence and cognitive function after controlling for confounding variables, including the onset of illness and comorbid cognitive functioning in Australian patients with an established *International Classification of Diseases-10* (ICD-10) diagnosis of psychotic disorder. Sanchez-Torres et al. (2013) used a longitudinal study to examine the impact of lifetime and current cannabis use on cognition in 42 patients with schizophrenia and found a negative effect of longitudinal cannabis use specifically in the social cognition domain (Pearson correlation, -0.34 ; $p < 0.05$). van Winkle et al. (2011) found that cannabis use before the onset of psychosis interacted significantly with the rs2494732 single nucleotide polymorphism of the AKT1 gene to affect patient reaction time and accuracy as measured by the Continuous Performance Test. Cannabis-using patients with the a priori vulnerability (i.e., homozygous for the polymorphism) were slower and less accurate on the CPT than nonusers.

Discussion of Findings

With regard to the effects of cannabis use on positive symptoms, the data are considered mixed. Studies report both worsening and no effect of cannabis use on positive symptoms in schizophrenia. The limitations observed in the reviewed studies included variable adjustment for other drug use and baseline symptom severity; issues with study design (observational); a reliance on self-reports; and variable analyses of cannabis use (i.e., dose/amount/frequency, current versus lifetime). However, these

studies, combined with human experimental studies demonstrating that cannabis can worsen positive symptoms in patients with schizophrenia, were also considered when determining the strength of evidence. With regard to negative symptoms, the data reviewed were generally more homogenous, with most studies reporting either an absence of association between cannabis use and negative symptoms or else reduced negative symptoms in cannabis users. Variable adjustments for other drug use and baseline symptom severity were noted as limitations in some studies. Overall, the data provide support for the conclusion that cannabis use does not worsen negative symptoms in patients with psychotic disorders. With regard to cognition in patients with psychotic disorders, the data reviewed in the systematic reviews suggest better cognitive performance in some cognitive domains in patients with psychotic disorders and cannabis use disorders, and in patients with a history of cannabis use, as compared to patients with psychotic disorders and no cannabis use disorder diagnosis. The limitations of two of the systematic reviews—Yucel et al. (2012) and Rabin et al. (2011)—include their study design (cross-sectional only); variable adjustments made for confounders, including other drug use; and variable definitions and inclusion criteria for cannabis using and non-using control groups. This study found better cognitive performance only in subjects with a lifetime history of cannabis use, but not recent cannabis use. The systematic review by Donoghue and Doody (2012) focused on longitudinal studies in schizophrenic subjects with and without comorbid cannabis use and found that cannabis users performed better on some measures of cognition, including verbal learning and memory, attention and psychomotor speed, and global cognitive factor tests, than non-cannabis users. The three reviewed studies showed similar effects; however, the largest study was more precise and had narrower confidence intervals. Estimates for the size of the effect are small to moderate. The primary articles reviewed indicate more mixed results than the systematic reviews.

Overall, the totality of data favor the conclusion that a history of, but not recent, cannabis use is associated with statistically significant performance improvement on measures of cognitive function in patients with psychotic disorders. It is not clear how the difference in scores might translate with respect to overall improved outcomes in functioning beyond the test setting. Furthermore, other data do not support the notion that acute cannabis exposure improves cognitive performance in patients with psychotic disorders, as acute intoxication is associated with impaired cognitive performance in cognitive domains of memory, learning, and attention (see Chapter 11). Among the multiple potential explanations of the data indicating better performance on certain measures of cognition in patients using cannabis are that these patients represent a higher-functioning sub-

group of psychotic patients or that cannabis users who achieve abstinence have better premorbid cognitive status. Additionally, it has been proposed that a history of cannabis use may have exerted neuroprotective effects in patients with psychotic disorders. Finally, we find insufficient data from which to draw conclusions regarding the effects of cannabis on risk for suicide in patients with psychotic disorders.

CONCLUSION 12-2

- 12-2(a) There is moderate evidence that, among individuals with psychotic disorders, there is a statistical association between a history of cannabis use and better cognitive performance.**
- 12-2(b) There is limited evidence of a statistical association between cannabis use and an increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders.**
- 12-2(c) There is moderate evidence for no statistical association between cannabis use and worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders.**

BIPOLAR DISORDER

Bipolar and related disorders are categorized by episodes and/or symptoms of mania, hypomania, and depression (APA, 2013). The risk factors for developing bipolar disorder are not clear; however, research suggests that brain structure, genetics, and family history may contribute to its onset (NIMH, 2016). Given that cannabis is reportedly the most commonly used illicit drug by individuals with bipolar disorders (Zorrilla et al., 2015), it is worthwhile for this report to explore the potential association between cannabis use and the development and course of bipolar disorder.

Is There an Association Between Cannabis Use and the Development of Bipolar Disorder or Mania?

Systematic Reviews

The committee identified one systematic review, Gibbs et al. (2015), that assessed the association between cannabis use and bipolar disorder.

der or mania. The authors searched multiple databases for English language studies published through 2014 and included studies that were experimental, prospective, cohort, or longitudinal. The overall search strategy yielded six studies with a total of 14,918 participants who met the inclusion criteria. Two of these studies, published in 2006 ($n = 4815$) and 2010 ($n = 705$), were used in the analysis. The meta-analysis showed an association between cannabis use and new onset of manic symptoms in individuals without preexisting bipolar disorder (OR, 2.97; 95% CI = 1.80–4.90). However, the researchers did not report information about the patient characteristics, the total number of subjects, age, gender, cannabis form, the ascertainment of mania symptoms, or other features of the two studies. Furthermore, due to the low number of studies that contributed to their research findings, the authors describe their conclusions as preliminary and tentative.

Primary Literature

Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)⁹ (Feingold et al., 2014) found that any past-year use of cannabis was associated with the onset of bipolar disorder (OR, 2.24; 95% CI = 1.44–3.51) in unadjusted analyses. However, after adjusting for sociodemographic and clinical variables, the association was attenuated and no longer statistically significant (aOR, 1.17; 95% CI = 0.65–2.11).

Using the same NESARC dataset as Feingold, Cogle and colleagues (2015)¹⁰ found that the risk of a past-year bipolar disorder diagnosis was elevated in regular (e.g., weekly use) cannabis users at Wave 2 follow-up: (OR, 1.37; 95% CI = 1.11–1.69). Cogle and collaborators (2015) reminded readers about the correlational nature of the study design and noted that causality could not be inferred from their conclusions. They also cautioned that the increased risk in bipolar disorders might be due to augmenting the psychotic features in frequent cannabis users (i.e., manic symptoms) that need further investigation. Also, Cogle and collaborators (2015) warned that in adjusting for other psychiatric comorbidities they only adjusted for those that fulfilled diagnostic thresholds, not other psychiatric symptoms that could explain the relationships of interest.

⁹ The NESARC is a longitudinal and nationally representative survey. Data on psychiatric disorders and quality of life were assessed from two waves of subjects. Wave 1: 2001–2002, $n = 43,093$; Wave 2: 2004–2005, $n = 34,653$.

¹⁰ Cogle et al. (2015) and Feingold et al. (2014) used the same dataset, but they chose to use different outcome variables: one analyzed past-year cannabis use, while the other examined past-year weekly cannabis use.

Discussion of Findings

Overall there is some evidence to support the association between cannabis use and the increased incidence of bipolar disorders. Although there is support for this association, more information is needed on the potential mediators that could explain the relationship as well as whether the risk is likely to occur only in conjunction with the use of other substances such as alcohol or nicotine. For example, panel studies that have evaluated the relationship found the magnitude of the relationship to be similar, but once alcohol or other substances were adjusted for in the statistical models, the associations diminished or became insignificant. This suggests that the constellation of behaviors that includes the use of cannabis, alcohol, and other substances might all play roles in the risk for bipolar disorders, with those different roles being difficult to disentangle. See Box 12-1 for additional discussion on the complex relationship between substance use and mental health disorders.

CONCLUSION 12-3 There is limited evidence of a statistical association between cannabis use and the likelihood of developing bipolar disorder, particularly among regular or daily users.

**Is There an Association Between Cannabis Use and
the Course or Symptoms of Bipolar Disorder?**

Systematic Reviews

The committee identified Gibbs et al. (2015) as a systematic review that assessed the relationship between cannabis use and the course, symptoms, or other endpoints in individuals with bipolar disorder. Gibbs et al. (2015) concluded, based on their narratives of three studies, that cannabis use may worsen the course of bipolar disorder by increasing the likelihood, severity, or duration of manic phases. Their narrative summarizes the findings of the three studies: the duration of active cannabis use was associated with duration of mania syndrome/symptoms; cannabis use within a quarter (3-month time period) was associated with manic symptoms or episodes; and a report of “any cannabis use” was associated with mania symptoms over 1 year in a sample of 3,426 inpatients and outpatients. The three studies were published in 2000, 2008, and 2009. The studies used clinical samples of 50 new-onset bipolar patients ages 16 to 54, 166 first-episode DSM-IV bipolar I patients ages 18 to 72, and 3,426 bipolar inpatients and outpatients (age not reported). No other information (gender, country, etc.) about the study populations was reported.

Primary Literature

Zorrilla and colleagues (2015), using the European Mania in Bipolar Longitudinal Evaluation of Medication study ($n = 1,922$ patients), showed that previous users of cannabis had similar outcomes to never users (all $p > 0.05$) in terms of bipolar disorders, whereas current users had lower rates of recovery ($p = 0.004$) and remission ($p = 0.014$) and higher rates of recurrence of bipolar disorder ($p = 0.014$). They also demonstrated that the median time to remission was longer in the current cannabis use group (571 days, 95% CI = 539–588) compared with the other two groups (never users: 236 days, 95% CI = 209–345; previous users: 189 days, 95% CI = 1.5–357), while the times to relapse and recurrence were shorter in current use group. Using Cox regression models, Zorrilla and colleagues (2015) found that cannabis use (versus no use) was associated with time to recovery (HR, 0.53; 95% CI = 0.298–0.959), relapse (HR, 1.61; 95% CI = 1.116–2.316), and recurrence (HR, 1.67; 95% CI = 1.206–2.320). However, when alcohol and other substance use variables were included in the model as confounders, only the time to recurrence remained significantly associated with cannabis use (HR, 1.47; 95% CI = 1.030–2.092).

Using the NESARC data with two waves, Feingold et al. (2014) examined the relationship between weekly cannabis use and almost daily cannabis use and found a steady association with the incidence of mania/hypomania symptoms in all adjusted models (OR, 2.47; 95% CI = 1.03–5.92). In contrast, daily cannabis use was not associated with mania/hypomania symptoms (OR, 0.52, 95% CI = 0.17–1.55).

Discussion of Findings

The evidence on the association between cannabis use and the course and symptoms in patients with bipolar disorder is modest, but it is suggestive that cannabis use moderates the course of bipolar disorder by increasing the time to recovery, relapse, and recurrence of manic phases. As discussed in the section above, when adjustments for alcohol and other substance use variables are included in the model as confounders, only the time to recurrence remains as significantly associated to cannabis use. There is also moderate evidence that weekly cannabis use to almost daily cannabis use can lead to the onset of mania/hypomania symptoms in adjusted models, but there is less evidence of this association for daily users of cannabis. The authors report that, given the inconclusive nature of the relationship between very frequent cannabis use (daily/almost daily) or less than weekly cannabis use and the onset of mania/hypomania symptoms in adjusted models (i.e., dose–response), other factors that have not been identified might mediate the relationship. The authors suggest that part of the problem of being able to find a conclusive

relationship between the frequency of cannabis use and mania or hypomania symptoms might be due to the resemblance of mania and hypomania symptoms to psychotic symptoms, making it difficult to discriminate between these types of symptoms. It should also be noted that in some of the studies reviewed above, the analyzed patient populations were undergoing treatment for bipolar disorder, adding an additional layer of limitations to the research findings.

In reviewing the literature on the relationship between cannabis use and bipolar disorder, the committee identified various limitations in the studies discussed above, including a lack of biogenetic covariates that could relate to both cannabis use and bipolar disorders, as well as other psychological symptoms that are not adjusted in these studies. Many of these studies do not take into account the variance among the subtypes of cannabis or in the potency or route of administration, all of which could lead to difference in results. Also, the lack of precision in measuring the frequency of cannabis use at baseline and in measuring follow-up data remains a problem.

CONCLUSION 12-4 There is moderate evidence of a statistical association between regular cannabis use and increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders.

DEPRESSION

Depression is one of the nation's most common mental health disorders (ADAA, 2016). Across the many depressive disorders that exist (e.g., persistent depressive disorder, major depressive disorder, premenstrual dysphoric disorder) there are common symptomatic features of feelings of sadness, emptiness, or irritable mood, accompanied by somatic and cognitive changes that affect the individual's capacity to function (APA, 2013, p. 155). The endocannabinoid system is known to play a role in mood regulation (NIDA, 2015); therefore, the committee decided to explore the association between cannabis use and depressive disorders or symptoms.

Is There an Association Between Cannabis Use and the Development of Depressive Disorders or Symptoms?

Systematic Reviews

The committee identified two systematic reviews that assessed the association between cannabis use and the risk of developing depressive

disorders or symptoms: Lev-Ran et al. (2013) and Moore et al. (2007). The most recent systematic review is discussed.

Lev-Ran et al. (2013) searched the published literature through 2012 and included studies with: population-based data that were collected longitudinally and prospectively; an exposure variable referring specifically to cannabis use (not “substance use”); outcome measures that referred specifically to depression—and not, for example, mixed anxiety–depressive symptoms; the outcome variable (depression) controlled for at baseline, or individuals with baseline depression being excluded; and data either presented as odds of developing depression following cannabis use or that allowed the OR to be calculated. When the authors identified multiple studies reporting on the same population cohort at different time points, only one study (the most recent) reporting on the respective cohort was included. The authors identified 14 studies published between 1977 and 2012. Seven were conducted in the United States, and one each were conducted in Australia, Canada, Colombia, the Netherlands, New Zealand, Norway, and Sweden. Sample sizes ranged from 736 to 45,087, with 10 of the samples having 1,000 or more participants. The ages of patients at cannabis assessment included high school age, subjects ages 12 to 17 or 12 to 16, and older groups ages 18 to 64. A wide range of measures were used to assess cannabis use: namely, any cannabis use in the previous 30 days; any previous cannabis use; cannabis use disorder; cannabis use one or more times per month; any cannabis use in the previous year or heavy use (at least once per week in the previous month); at least five previous occasions of cannabis use or heavy use (at least weekly); any use in the previous 6 months; or more than 4 occasions of use per month in a 5-year period. Studies also varied in the definition of comparison groups, with some studies contrasting any cannabis use to no cannabis use, and other studies comparing “heavy cannabis use” to a group with some or no cannabis use. Thus, the comparison group (lower level of exposure to cannabis) in the latter studies included nonusers, as well as individuals using cannabis less than weekly, or individuals not having a cannabis use disorder. Studies varied in their approaches to adjust for confounding factors, ranging from none to adjustment for more than 20 variables. One half of the studies accounted for other types of substance use and/or mental health issues as potential confounders. The analysis showed that cannabis use was associated with a small increase in risk for depressive outcome (pOR, 1.17; 95% CI = 1.05–1.30). The analysis further revealed a dose–response relationship, with a slightly higher OR observed in seven studies comparing heavy cannabis use to non-cannabis users (pOR, 1.62; 95% CI = 1.21–2.16).

Primary Literature

Although several primary research studies found a positive association, the confounding factors of polydrug use or unspecified cannabis use made it difficult for the committee to make conclusions on the overall findings (Brook et al., 2016; Nkansah-Amankra and Minelli, 2016; Rasic et al., 2013). Additional studies reviewed provided mixed findings on the association between cannabis use and depression or depressive symptoms (Crane et al., 2015; Gage et al., 2015; Silins et al., 2014; Wilkinson et al., 2016). A consideration of the confounding factors led to several of these mixed findings. For example, Sillins et al. (2014) published an analysis of interview data from three longitudinal studies from Australia and New Zealand. The investigators sought to determine the association between the maximum frequency of cannabis use before age 17 and seven developmental outcomes, including depression. The number of participants varied by the outcome assessed but ranged from $n = 2,537$ to $3,765$. Because this was an integrated study, the outcomes of depression were assessed by different measures (i.e., Composite International Diagnostic Interview, Clinical Interview Schedule, and short-form Depression Anxiety Stress Scale) and at different ages across the three studies. The investigators of this study created a dichotomous measure of moderate or severe depression in the past week to the past month between ages 17 and 25 years. Using combined data adjusted for study-specific effects, the investigators found a significant association between adolescent cannabis use and the study's measure of depression (less than monthly use, OR, 1.12; 95% CI = 1.01–1.25; monthly or more, OR, 1.26; 95% CI = 1.02–1.56; weekly or more, OR, 1.42; 95% CI = 1.03–1.94; daily use OR, 1.59; 95% CI = 1.04–2.42), as well as an apparent potential dose–response relationship. However, after adjusting for relevant covariates in the analysis, this association became insignificant and negligible in size (less than monthly use, aOR, 1.01; 95% CI = 0.85–1.19; monthly or more, aOR, 1.01; 95% CI = 0.72–1.42; weekly or more, aOR, 1.02; 95% CI = 0.61–1.69; daily use, aOR, 1.02; 95% CI = 0.52–2.01). The authors noted that the confounding factors spanning the individual's background and functioning as well as parental and peer factors likely affected the change in the research findings.

Discussion of Findings

The evidence reported suggests that cannabis use, and particularly heavy cannabis use, is associated with a small increase in the risk of developing depressive disorders. This evidence is supported by a good-quality recent systematic review that included 10 longitudinal studies with sample sizes between 700 and 45,000. Although the supplemental studies from the primary literature reported mixed findings, the commit-

tee concludes that there is a strong enough evidence base to support the conclusion that there is an association between cannabis use and a small increased risk (pOR of 1.17; Lev-Ran et al., 2013) of developing depressive disorders, which increases with increased frequency of use (OR of 1.62; Lev-Ran et al., 2013). The possible relationship between heavy cannabis use and the development of depressive disorders or symptoms needs to be further explored.

Given that these relationships are associational and not necessarily causal, it is important to note possible alternative explanations for the mixed findings. For example, within the literature, a reverse association between cannabis use and depressive disorders has been documented, and the relationship may be bidirectional (Horwood et al., 2012; Wilkinson et al., 2016). This complex scenario is consistent both with the known protective roles of the endocannabinoid system in the control of mood and affect and with the propensity of cannabinoid receptors to undergo desensitization following prolonged activation. See Box 12-1 for an additional discussion on this topic.

To review the research on the potential therapeutic effects of cannabis or cannabinoids on major depression disorder, please refer to Chapter 4 (Therapeutic Effects of Cannabis and Cannabinoids).

CONCLUSION 12-5 There is moderate evidence of a statistical association between cannabis use and a small increased risk for the development of depressive disorders.

Is There an Association Between Cannabis Use and the Course or Symptoms of Depressive Disorder?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the course, symptoms, or other endpoints in individuals with a depressive disorder.

Primary Literature

The committee did not identify any good-quality primary literature that reported on the association between cannabis use and the course, symptoms, or other endpoints in individuals with a depressive disorder and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

CONCLUSION 12-6 There is no evidence to support or refute a statistical association between cannabis use and changes in the course or symptoms of depressive disorders.

SUICIDE

Suicide is the act of purposely taking one's own life. It is the 10th most common cause of death in the United States, with an estimated 13 suicidal deaths per 100,000 individuals; it is often related to mental illness, substance abuse, or a major stressful event (CDC, 2014; MedlinePlus, 2016). Cannabis is widely used for both medical and recreational purposes (Azofeifa et al., 2016), and therefore, there is a public health interest to evaluate the possible association between cannabis use and suicide, suicidal attempts, and suicide ideation.

Is There an Association Between Cannabis Use and Suicidal Ideation, Suicide Attempts, and Suicide?

Systematic Reviews

Two systematic reviews were identified that assessed the association between cannabis use and suicidal ideation, attempts, and suicide (Borges et al., 2016; Moore et al., 2007). We report here on the most recent one. Borges et al. (2016) conducted a systematic review to address multiple questions concerning acute and chronic cannabis use, suicidal ideation, suicide attempts, and suicide. The authors reported the databases searched and their search terms, but they did not report the number of citations screened or the reasons for exclusions. The term "any cannabis use" was defined as: life-time use, use before or at age 15, ever used, any use in past 30 days, or any use in the last year. "Chronic use" was referred to as: cannabis use patterns, symptoms of cannabis use disorder, and heavy cannabis use. "Heavy cannabis use" was defined as: used 40 or more times, DSM-III-R abuse/dependence, ≥ 6 times per month, >11 times in past year, >10 times, or daily.

The authors reviewed 12 studies that were relevant to the committee's research question. Their meta-analysis of six studies showed that any cannabis use was associated with an increased risk of suicidal ideation (pOR, 1.43; 95% CI = 1.13–1.83). Similarly, a review of five studies showed that heavy cannabis use was also associated with a larger increase of suicidal ideation (pOR, 2.53; 95% CI = 1.00–6.39). The six studies included in the meta-analysis of any cannabis use and suicide ideation were published between 1997 and 2014 and conducted in Canada, New Zealand, Norway, and the United States (four studies) in populations of male and

female young adults or adolescents. The five studies included in the meta-analysis of heavy cannabis use and suicidal ideation were published between 1997 and 2013 and conducted in Canada, New Zealand, Norway, and the United States (two studies) in male and female populations of all age groups.

The authors also assessed another subset of six studies to determine the association between any cannabis use and suicide attempts, reporting a pOR of 2.23 (95% CI = 1.24–4.00). The studies used reported on male and female adolescents or young adults in Canada, Ireland, and the United States (four studies). A review of a third subset of six studies found a higher risk of suicide attempt associated with heavy cannabis use (pOR, 3.20; 95% CI = 1.72–5.94). These six studies reported on male and female adolescents, young adults, or adults in Canada, New Zealand/Australia (two studies), Norway, and the United States (two studies).

The researchers reported that any cannabis use was associated with an increased risk of death by suicide (pOR, 2.56; 95% CI = 1.25–5.27), based on a meta-analysis of four nonoverlapping studies. The studies included two case-control studies and two longitudinal studies published between 2003 and 2012, which were conducted in Colombia, Denmark, Sweden, and the United States; the studies were carried out in young adults and in all age groups, in males and females, and in male-only study groups. Interestingly, the one study restricted to males only showed no association of cannabis with suicide, but the other studies that used mixed groups of males and females did show an association of cannabis with suicide.

Primary Literature

The committee identified one recent primary article published in 2016 (Shalit et al., 2016) that reported on the association between cannabis use and the risk of suicidality (suicidal ideation and suicide attempt). Shalit and collaborators presented their results using a general population sample of the NESARC ($n = 34,653$; 963 cannabis users versus 30,586 nonusers). They found that in the general population, any cannabis use in Wave 1 (baseline) was not statistically significantly associated with increased risk for developing suicidality in Wave 2 (follow-up) (aOR, 1.56; 95% CI = 0.98–2.46). However, when the results were stratified by gender, the researchers found significant differences in risk for suicidality. Among men, any cannabis use was significantly associated with the incidence of suicidality in fully adjusted models (aOR, 1.91; 95% CI = 1.02–3.56), but not for women (aOR, 1.19; 95% CI = 0.64–2.20). The magnitude of the relationship with the 3-year incidence of suicide ideation is larger in men (aOR, 4.28; 95% CI = 1.32–13.82) who are daily cannabis users, but this pattern is not observed for women (aOR, 0.75; 95% CI = 0.28–2.05).

However, in adjusted models neither cannabis use (aOR, -1.91 ; 95% CI = $0.85-4.28$) nor daily cannabis use (aOR, 1.13 ; 95% CI = $0.42-3.05$) was statistically significantly associated with the incidence of suicide attempts. Another finding of importance was that sex moderated the association between cannabis use, particularly daily use, and suicide attempts, with a significantly increased dose-response relationship in men (any cannabis use OR, 3.35 ; 95% CI = $1.07-10.47$; daily cannabis use OR, 32.31 ; 95% CI = $2.59-402.88$). However, there are several limitations, including that suicidality was only assessed in participants who reported a 2-week period of depressed mood or anhedonia, so the results might underestimate the effect for those that have suicidal ideation or suicide attempts without these symptoms. Other limitations include the use of dichotomous response categories for suicidality when there is some evidence that additional changes to the measures are needed; the lack of adjustment for some early traumatic life events associated with suicidality; and the lack of adjustments for psychotic disorders.

Discussion of Findings

The evidence reported suggests that any cannabis use is related with increased suicidal ideation, augmented suicide attempts, and greater risk of death by suicide. The studies presented demonstrate evidence of a dose-response effect, with heavy cannabis use being associated with a higher risk of suicidal ideation and suicidal attempts. Additionally, sex differences emerged from the research findings related to suicidality (Shalit et al., 2016) and death by suicide (Borges et al., 2016). These sex differences may have occurred due to differences in where the study samples were recruited (e.g., Australia, Canada, Denmark, New Zealand, Norway, Sweden, United States, etc.) or how the data were assessed. This might suggest that sample composition, gender, and the type of assessment could matter when examining these associations between cannabis use and suicidality and suicide completion.

Although the evidence seems to support a relationship between cannabis use and suicidality, particularly heavy cannabis use and suicidality, the limitations of the literature temper such findings. Several limitations should be noted, including the lack of homogeneity in the measurement of cannabis exposure, the lack of systematic controls for known risk factors, the short period of observation for suicidality, the variability in the covariates used to adjust for confounders, the differences in the dose-response analyses, and problems of small sample size. Additionally, as reported by the authors, some studies adjust for alcohol and other comorbidities, while in other studies there is no report of such adjustments. There is a strong need for new studies that discriminate between the acute and the

chronic use of cannabis and between suicidal ideation, suicide attempts, and completed suicides.

CONCLUSION 12-7

12-7(a) There is moderate evidence of a statistical association between cannabis use and increased incidence of suicidal ideation and suicide attempts, with a higher incidence among heavier users.

12-7(b) There is moderate evidence of a statistical association between cannabis use and increased incidence of suicide completion.

ANXIETY

Anxiety disorders share features of excessive fear and anxiety, which induce psychological and physical symptoms that can cause significant distress or interfere with social, occupational, and other areas of functioning (APA, 2013). In a given year, an estimated 18 percent of the U.S. adult population will suffer from symptoms associated with an anxiety disorder (NIMH, n.d.). Given the role of the endocannabinoid system in mood regulation, it is worthwhile for this report to explore the relationship between anxiety and cannabis.

Is There an Association Between Cannabis Use and the Development of Anxiety Disorders?

Systematic Reviews

One systematic review was identified that assessed the relationship between cannabis use and anxiety disorders (Kedzior and Laeber, 2014). The authors searched two databases for articles published through 2013 to identify studies that had been conducted in noninstitutionalized populations, with anxiety diagnoses based on DSM/ICD criteria, with odds ratios or data sufficient for the calculation of effects, and with comparison data from healthy nonusers. They then identified five studies that examined cannabis use at baseline and anxiety at follow-up. The five studies were all longitudinal, published between 1996 and 2013, and conducted in Australia, Colombia, the Netherlands, New Zealand, and the United States. Sample sizes were more than 2,000 or greater in four studies and more than 12,000 in the fifth study. Four studies were of adolescents and a fifth studied the general population (age unspecified). The five studies

adjusted for confounders such as demographics, prior anxiety disorder diagnosis, alcohol and tobacco use, and other mental health problems at age 15. In their review of the five studies, Kedzior and Laeber (2014) found that cannabis use at baseline was associated with the development of symptoms of anxiety at follow-up (OR, 1.28; 95% CI = 1.06–1.54) after adjusting for confounders (e.g., other substance use, psychiatric comorbidity, certain demographics).

Primary Literature

In a longitudinal U.S. study of a nationally representative sample of adults 18 years or older (NESARC; $n = 34,653$), Blanco and colleagues (2016) investigated the prospective associations of cannabis use in the past 12 months (Wave 1; years 2001–2002); with anxiety disorders 3 years later (Wave 2; years 2004–2005); and adjusted for sociodemographic characteristics, family history of substance use disorder, disturbed family environment, childhood parental loss, low self-esteem, social deviance, education, recent trauma, past and present psychiatric disorders, and respondent's history of divorce. The researchers found that cannabis use in the 12 months preceding the survey was not associated with an increased prevalence of anxiety disorders (OR, 1.0; 95% CI = 0.8–1.2) after adjustments for covariates. The researchers also reported no significant relationship of cannabis use (Wave 1) with the prevalence of panic disorder (OR, 0.8; 95% CI = 0.5–1.2), social anxiety disorder (OR, 1.2; 95% CI = 0.8–1.8), specific phobia (OR, 0.9; 95% CI = 0.7–1.2), or generalized anxiety disorder (OR, 1.0; 95% CI = 0.7–1.4) assessed 3 years later (Wave 2). The researchers also found no significant relationship between cannabis use and incident anxiety disorders (aOR, 0.9; 95% CI = 0.7–1.1). However, they did find that an increased frequency of cannabis use was related with significantly increased odds of incident social anxiety disorder (OR, 1.8; 95% CI = 1.1–2.8). Some of the limitations of this study are that cannabis use was ascertained by self-report, causality could not be established because of the possibility of residual confounding, and the follow-up period was limited to 3 years.

Feingold and colleagues (2016) used the same dataset as Blanco et al. (2016), NESARC, and also found no association of cannabis use with the increased incidence of any anxiety disorder (aOR, 1.12; 95% CI = 0.63–0.98) after adjusting for covariates. However, they did find a statistically nonsignificant association between daily or almost daily use of cannabis at Wave 1 (baseline) with the incidence of social anxiety at follow-up 3 years later (aOR, 1.98; 95% CI = 0.99–6.98). This relationship was found to be significant in older adults (aOR, 2.83; 95% CI = 1.26–6.35) but not for younger adults (aOR, 1.76; 95% CI = 0.44–6.98). They also found a

significant relationship between cannabis use disorder at baseline and incident social anxiety disorder among young adults (aOR, 2.45; 95% CI = 1.19–5.06) but not older adults (aOR, 1.38; 95% CI = 0.58–3.25). No other associations between cannabis use disorder and other anxiety disorders proved to be significant after adjustment for covariates.

Cogle et al. (2015) also used the NESARC to examine past-year regular cannabis use (defined as at least weekly use) and current and prospective presence of anxiety disorders 3 years later. These authors found no association (OR, 1.09; 95% CI = 0.90–1.32) in the prospective analyses that adjusted for psychiatric comorbidity and sociodemographic factors. However, when looking at specific anxiety disorders, Cogle and colleagues (2015) report finding a relationship between regular cannabis use and an increased risk of developing panic disorder with agoraphobia (OR, 1.56; 95% CI = 1.11–2.19) and social phobia (OR, 1.89; 95% CI = 1.54–2.32). As with other studies using the NESARC, the authors emphasize the non-randomized nature of the study design, the possibility that the study was underpowered to find certain relationships, and the relatively short time period of observation.

Bechtold and colleagues (2015), using data from the oldest cohort of the Pittsburgh Youth Study, found that there were no differences among cannabis trajectory groups (categorized as low/nonusers, adolescence-limited users, increasing users, and early onset chronic users) related to a lifetime diagnosis of anxiety disorders for black or white men after controlling for confounders (e.g., socioeconomic status, co-occurring use of other substances, physical and mental health problems that predated cannabis use, and access to medical care). In this study cannabis use was evaluated with the Substance Use Questionnaire, with respondents (who were ages 15 to 26) initially indicating the number of days they had used cannabis in the previous 6 months and then, in each of the subsequent 10 annual follow-ups, reporting their use in the previous year. At age 36, respondents were assessed with the Diagnostic Interview Schedule to determine whether they had ever met the criteria for an anxiety disorder, and an analysis shows that the patterns of cannabis use from adolescence to young adulthood were not related to anxiety disorders. However, the authors mentioned several limitations, including the possibility of selection effects; the fact that cannabis use was determined by self-report; and the use of a limited sample that used cannabis from one geographic area and included only white and black men, implying that the results might not be generalizable to the general population. A recent study by Gage and colleagues (2015) found similar results. Using data from the Avon Longitudinal Study of Parents and Children (a UK birth cohort study), they found no evidence of an association between cannabis use at age 16 and anxiety disorder at age 18 (aOR, 0.96; 95% CI = 0.75–1.24) after

adjusting for pre-birth and childhood confounders (family history of depression, maternal education, urban living, IQ, borderline personality traits, victimization, peer problems, conduct disorder, and other substance use). The authors cite as limitations of their study the use of self-reported data, poor follow-up rates, and a limited power to detect small effects.

Brook and colleagues (2014), using the Harlem Longitudinal Developmental Study, assessed urban African American and Puerto Rican participants ($n = 816$) with four waves of data. In this study, Brook et al. (2014) found that participants with joint chronic cannabis, tobacco, and alcohol use were at an increased risk for generalized anxiety disorder in adulthood when compared to those with occasional alcohol use and no smoking and no cannabis use (OR, 4.35; 95% CI = 1.63–11.63). Again, this study's limitations, such as the use of self-reports, the use of proxies to determine earlier generalized anxiety disorder (depression in Time 1), and omitted variables (such as family substance use), could have explained such relationships.

Additional work by Brook and colleagues (2016) reported on a large community-based sample (the Children and Adults in Community study, $n = 973$ at Time 1), examining comorbid trajectories of substance use which included conjoint chronic cannabis with chronic alcohol and cigarette use as predictors of generalized anxiety disorder. According to their multivariate logistic regression analyses, the Bayesian posterior probability (BPP) of members who were chronic or moderate to heavy users of cannabis, alcohol, and cigarettes—when compared to the patterns of those with occasional alcohol use and no smoking and no cannabis—had an aOR of 6.39 (95% CI = 2.62–15.56). This suggests that the conjoint use of cannabis with alcohol and cigarettes could have biological or psychosocial effects that increased the risk for generalized anxiety disorder. However, the study had several limitations in the present study, including having a mostly white sample from upstate New York and not including environmental or social variables that could explain the relationship under study, such as family substance use or childhood psychiatric disorders.

Discussion of Findings

Studies examining the relationship between cannabis use and anxiety disorder show mixed results depending on whether they assessed the development of anxiety symptoms or the incidence of anxiety disorders; whether the explanatory variable was any cannabis use or cannabis use disorder; and whether there were adjustments for psychiatric comorbidity and sociodemographic factors. For example, Kedzior and Laeber (2014) found that cannabis use at baseline was associated with the development of symptoms of anxiety at follow-up. In contrast, the 2016 report

by Blanco and colleagues, the 2015 report by Cogle et al., and the 2015 report by Gage and colleagues all found no association between cannabis use and an increased prevalence of anxiety disorders in adjusted models. However, both Feingold et al.'s and Blanco et al.'s studies did find an association of daily or almost daily use of cannabis at Wave 1 with the incidence of social anxiety disorder at follow-up 3 years later. Age seemed to moderate this relationship since it was found to be significant in older adults but not in younger adults.

Some of the limitations of these studies are that cannabis use was ascertained by self-report; that causality cannot be established because of the possibility of residual confounding; that the follow-up period was limited to 3 years; and that there was a high loss in the follow-up and limited power to detect small effects. Further work needs to be done to examine why the outcomes differ depending on whether the assessment is done with anxiety symptoms or anxiety disorders and whether the explanatory variable is any cannabis use or cannabis use disorder. Moreover, studies are needed to determine whether psychiatric comorbidity, sociodemographic factors, or the conjoint use of cannabis with alcohol and cigarettes have biological or psychosocial effects that increase the risk for generalized anxiety disorder.

To review the research on the potential therapeutic effects of cannabis or cannabinoids on anxiety, please refer to Chapter 4 (Therapeutic Effects of Cannabis and Cannabinoids).

CONCLUSION 12-8

12-8 (a) There is limited evidence of a statistical association between cannabis use and the development of any type of anxiety disorder, except social anxiety disorder.

12-8 (b) There is moderate evidence of a statistical association between regular cannabis use and increased incidence of social anxiety disorder.

Is There an Association Between Cannabis Use and the Course or Symptoms of Anxiety Disorders?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the course, symptoms, and other endpoints of anxiety disorders.

Primary Literature

Recent work by Grunberg and collaborators (2015) conducted a prospective study to examine whether cannabis use (i.e., use during the past 30 days using the Time-Line Follow Back¹¹) moderates the effects of temperament on the level of anxiety symptoms (measured with Achenbach's System of Empirically Based Assessment) within late adolescence and early adulthood ($n = 338$; 18- to 21-year-olds). While there was no association between cannabis use groups and anxiety symptoms among the college students in this prospective study, the researchers conducted simple slope analyses investigating the relationship between harm avoidance (characterized by heightened apprehension, shyness, pessimism, and inhibition of behaviors) and prospective anxiety symptoms for those subjects who rated low (zero days of use out of 30 days) and high (approximately 26 days of use out of 30 days) on cannabis use. The researchers found that harm avoidance measured at baseline was associated with more symptoms of anxiety measured 1 year later—but only for those low in cannabis use ($\beta = 0.15$, $t(329) = 2.69$, $p < 0.01$). When cannabis use was high, harm avoidance was unrelated to anxiety ($\beta = -0.14$, $t(329) = -1.40$, $p = 0.16$). Study participants with higher cannabis use showed a positive association between novelty seeking and anxiety symptoms ($\beta = 0.28$, $t(329) = 3.46$, $p = 0.001$), while those lower in cannabis use showed no relation between novelty seeking and anxiety symptoms ($\beta = -0.08$, $t(329) = -1.61$, $p = 0.11$).

Discussion of Findings

Grunberg and collaborators (2015) warned, however, that the findings discussed above should be taken with caution since the mechanisms underlying these relations are still not clear. In addition, although this study uses a prospective design in which cannabis use and temperament are evaluated at baseline to predict anxiety symptoms 1 year later, it is limited to college students (ages 18–21) in only one assessment site. The authors emphasized that the reason the relationship between cannabis use and anxiety symptoms is inconsistent is that there was no consideration of cannabis effects on other factors that influence anxiety symptoms such as temperament (i.e., levels of harm avoidance and novelty seeking) within the sample. Some limitations of this study are the use of a college student sample, the use of self-report for all assessments, and the use of correlational data—although cannabis use and temperament were measured 1 year before anxiety symptoms. Given the limited evidence of studies that

¹¹ Authors describe this as a calendar-assisted structured interview that allows participants to indicate the amount of cannabis used on each day over the past month.

address the relationship between cannabis use and anxiety symptoms, these findings need to be replicated in larger samples with appropriate controls.

CONCLUSION 12-9 There is limited evidence of a statistical association between near daily cannabis use and increased symptoms of anxiety.

POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder (PTSD) falls within the broader trauma- and stressor-related disorders categorized by the DSM-V. The diagnostic criteria of PTSD include an exposure to a traumatic event (e.g., the threat of death, serious injury, or sexual violence) and exhibiting psychological distress symptoms that occur as a result of that exposure (e.g., intrusion symptoms, such as distressing memories; avoidance of stimuli that are associated with the traumatic event; negative alterations in mood and cognition; alterations in arousal and reactivity associated with the traumatic event; functional impairment) (APA, 2013, pp. 271–272). Given the known psychoactive effects of cannabis, the committee chose to explore the association between PTSD and cannabis use in this review.

Is There an Association Between Cannabis Use and the Development of PTSD?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the risk of developing PTSD.

Primary Literature

The committee did not identify any good-quality primary literature that reported on the association between cannabis use and the development of PTSD and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

CONCLUSION 12-10 There is no evidence to support or refute a statistical association between cannabis use and the development of posttraumatic stress disorder.

Is There an Association Between Cannabis Use and the Course or Symptoms of PTSD?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the course, symptoms, and other endpoints in PTSD.

Primary Literature

Gentes et al. (2016) found that past 6-month cannabis use was associated with increased PTSD severity (Clinician Administered PTSD Scale; global severity score; aOR, 1.30; 95% CI = 1.01–1.66), depressive symptoms (Beck Depression Inventory; aOR, 9.25; 95% CI = 1.13–1.75), and suicidality (Beck Depression Inventory Item 9; aOR, 4.63; 95% CI = 1.02–1.54) in a population of treatment-seeking veterans ($n = 719$). In this study, the odds ratios were adjusted for age, race, service era, and combat exposure, but not co-occurring substance use. Conversely, Manhapra et al. (2015) found improvements in PTSD symptoms (Mississippi Scale for Combat-Related Posttraumatic Stress Disorder), violence, and suicidality after 4 months of abstinence from cannabis relative to symptoms upon entry to the study in a large population of veterans admitted for an intensive PTSD program ($n = 22,948$). Villagonzalo et al. (2011), in a small study of patients ($n = 80$; mean age 35 years) participating in a methadone maintenance program, found that the severity of cannabis use was associated with the occurrence of certain PTSD symptoms, as measured by the Posttraumatic Stress Disorder Checklist–Civilian Version. Significant findings were identified for measures of reexperiencing (i.e., repeated disturbing dreams, $\chi^2(2) = 6.351$; $p < 0.05$; physical reaction at reminder of event $\chi^2(2) = 7.053$; $p < 0.05$; hyperarousal (i.e., difficulty concentrating, $\chi^2(2) = 7.517$; $p < 0.05$; “super alert” $\chi^2(2) = 6.778$; $p < 0.05$; easily startled $\chi^2(2) = 9.645$, $p < 0.01$); and overall PTSD symptoms (1-way ANOVA, $F(2,65) = 3.705$; $p < 0.05$).

Of interest, the committee also identified two large observational studies that compared the effects of cannabis to controls. Both studies enrolled predominately male veterans. A large cohort study (Wilkinson et al., 2015) examined outcomes for 2,276 veterans who received specialized intensive PTSD services between 1992 and 2011. Assessments for substance use and PTSD symptoms were taken at intake and at 4 months after discharge. Veterans who continued to use or started using cannabis after discharge had significantly worse PTSD symptoms and greater drug abuse than those who had never used or who had stopped cannabis use at 4 months after discharge ($p < 0.0001$). Starters also had more violent behavior in the 4 months after enrollment compared to other groups

($p < 0.0001$). There were no significant differences among the groups on employment status. A second study (Johnson et al., 2016) was a matched, case-control cross-sectional study that was conducted in 700 veterans with probable PTSD, half of whom used cannabis and half who were nonusers. Cannabis users and nonusers did not differ on PTSD symptom severity ($p = 0.91$) or depression severity ($p = 0.07$) as measured by the PTSD Checklist–Civilian Version and the Patient Health Questionnaire, respectively. However, cannabis users were more likely to experience suicidal ideation ($p = 0.04$) and reported more alcohol use ($p < 0.001$) as measured by the Paykel questionnaire, an Alcohol Timeline Followback assessment, and the Alcohol, Smoking, and Substance Involvement Screening Test.

Discussion of Findings

Notable in this section relative to the others in this chapter is the lack of data addressing the key questions posed by the committee. For example, using the committee's specified search strategy, we found no relevant studies that directly addressed the question of whether cannabis use is associated with an increased risk of PTSD. Of the relevant studies reviewed, cannabis use appears to be associated with more severe symptoms, but limited sample sizes were an issue in certain studies; that issue, combined with the lack of adjustment for baseline symptom severity and other drug use and the examination of specialized patient populations, limits the strength of the conclusions that can be drawn. Overall, there is limited evidence for an association between cannabis use and increased PTSD symptom severity. The direction of the association is difficult to address, however. It has been argued that PTSD is a risk factor for cannabis use, and cannabis-using patients with PTSD often cite symptom-coping motives for cannabis use, which suggests that more severe PTSD may be driving patients to increase cannabis use in an effort to self-medicate.¹² In contrast, one study (Manhapra et al., 2015) found overall improvements in several symptom domains after 4 months of abstinence from cannabis, suggesting that cannabis use may be causally related to more severe PTSD symptoms. See Box 12-2 for a discussion on why it is often difficult to conclude causality in the associations between substance use and mental health.

To review the research on the potential therapeutic effects of cannabis or cannabinoids on PTSD, please refer to Chapter 4 (Therapeutic Effects of Cannabis and Cannabinoids).

¹² Studies examining PTSD as a risk factor for cannabis use and cannabis use disorders were identified and are discussed in Chapter 13 of this report.

CONCLUSION 12-11 There is limited evidence of a statistical association between cannabis use and increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder.

RESEARCH GAPS

As noted above, we found a paucity of studies relevant to our key questions. To address the research gaps relevant to PTSD, the committee suggests the following:

- More longitudinal studies to determine whether cannabis use is associated with an increased incidence of PTSD.
- In patients with PTSD, current data do not provide a very clear picture as to whether cannabis use affects PTSD symptoms. More longitudinal studies examining the effects of cannabis use on PTSD symptoms need to be conducted, with a specific emphasis placed on detailed measures of cannabis use (amounts, potency, routes of administration), controls for baseline symptom severity and the use of other substances, and temporality (excluding patients with cannabis use at study entry).
- From a cannabis therapeutics perspective, blinded, randomized, placebo-controlled studies in patients with PTSD need to be conducted to evaluate any potential therapeutic benefits of cannabis on PTSD symptoms and course.
- There is also a research need to investigate cannabis and cannabis constituents (tetrahydrocannabinol and cannabidiol) in animal models.

SUMMARY

This chapter outlines the committee's efforts to review the current evidence base for the association of cannabis use with prioritized mental health conditions. The health conditions reviewed in this chapter include schizophrenia and other psychotic disorders, bipolar disorder, depression, suicide, anxiety, and PTSD. The committee formed a number of research conclusions related to these health endpoints; however, it is critically important that each of these conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections. See Box 12-3 for a summary list of the chapter's conclusions.

A conclusion weighted as substantial was reached for the research question addressing the statistical association between cannabis use and the development of schizophrenia or other psychoses. As noted in the

BOX 12-2
Special Considerations for Systematic
Reviews of Observational Studies

The quality assessment of the systematic reviews in this chapter followed the research methods used throughout this report within the context of the mental health literature. Of note, the primary literature in mental health is mostly observational (in contrast to the literature base in other fields, such as therapeutics), and it was not possible to restrict systematic reviews and meta-analyses to those that synthesized evidence from randomized clinical trials (RCTs). Accordingly, the vast majority of the studies included in the systematic reviews and meta-analyses summarized in this chapter were observational studies. In addition to receiving a lower-quality grading in most systems, the methodologic science around the synthesis of observational data is less developed than it is for RCTs. The methodology used for systematic reviews and meta-analysis originates in the synthesis of data from RCTs, where methodology is highly standardized and structured. The synthesis of observational studies presents some challenges that have not been fully met, arising out of the greater variety in study design and conceptualization and the fact that there has been generally less experience in applying the methodology of systematic reviews and meta-analysis to observational literature. For example, none of the systematic reviews discussed in this chapter mentioned a protocol, an ethics review board, or a priori published research objectives—features that have become increasingly standard in systematic reviews of RCTs. Mallen and colleagues (2006, p. 765) noted: “Quality assessment does not routinely occur in systematic reviews of observational studies. Where it does occur, there is no clear consensus in the method used.” Brugha and colleagues (2012, p. 450), in their review of systematic reviews and meta-analyses of observational psychiatric epidemiology studies, found “a number of deficiencies in the conduct and reporting of systematic reviews and meta-analyses of observational psychiatric epidemiology studies that could have serious implications for inferences drawn or decisions made on the basis of these reviews. There were frequent omissions of descriptions of method of abstraction, study quality, publication bias, bias and confounding.”

In assessing the body of evidence, it is tempting to correlate the number of systematic reviews with the strength of the evidence; however, a number of concerns arise when synthesizing evidence across systematic reviews. When multiple systematic reviews address similar research questions or slight variations on similar research questions, it is likely that the reviews will include some of the

chapter’s Discussion of Findings sections, there are common trends in the types of study limitations found in this evidence base. The most common are limitations in the study design (e.g., a lack of appropriate control groups, a lack of long-term follow-ups) variable analysis of cannabis use (i.e., dose/amount/frequency current versus. lifetime); small

same primary studies. For example, in the Schizophrenia section above, the three systematic reviews assessing the effects of cannabis on cognition—Donoghue and Doody (2012), Rabin et al. (2011), and Yucel et al. (2012)—each cite the primary study by Schnell et al. (2009). Another four studies were included in two of the systematic reviews on cognition. Given the use of some primary studies in more than one systematic review, the number of systematic reviews or meta-analyses may not, by themselves, indicate a stronger body of evidence.

While it is easy to understand how multiple reviews might identify similar studies, it is also of concern when reviews identify different studies. For example, the systematic review on cognition by Rabin et al. (2011) identified four studies that were not included in the reviews by Donoghue and Doody (2012) or by Yucel et al. (2012), and Yucel and colleagues (2012) also identified four studies that were not included in the other systematic reviews. This may be explained by a careful examination of the search strategies and inclusion/exclusion criteria, but the reasons for such differences are not always transparent.

Exposure measurement is always of concern in observational studies, and assessment of cannabis exposure is particularly fraught because of its illegal status (in most settings) and the reliance on self-report. Inherent difficulties in accurately assessing the exposure in terms of dose, specific chemicals, mode of intake, duration, frequency, and other variables result in the variability in definitions used to operationalize cannabis exposure. For example, systematic reviews may include studies using greatly differing definitions such as nondependent cannabis use in past week, a history of 0.5 g cannabis/day, cannabis use in the last 6 months, and >2g cannabis/week (Rabin et al., 2011). In addition, studies focusing on mental health may use medical records showing a diagnosis of cannabis use disorder as their exposure variable, either focusing on the disorder as a construct or as a proxy for cannabis exposure. This last approach allows researchers to consider the construct of cannabis use disorder, but it may result in exposure and non-exposure groups having similar intakes of cannabis. One can imagine a scenario where a person with a cannabis use disorder diagnosis has perhaps not consumed cannabis in the preceding week, month, or other time frame and where individuals without a diagnosis of cannabis use disorder had consumed cannabis in the same time frame. In this scenario, misclassification in both directions would result in biases toward the null, although differences between individuals with and without mental health diagnoses of cannabis use disorder could be expected to be associated with other differences observed in the study groups.

sample sizes; and research gaps in the studies of depression and PTSD. These limitations highlight the enormous amount of available opportunity to advance the current research agenda, in the hopes of providing comprehensive and conclusive conclusions on the potential harms and therapeutic benefits of cannabis or cannabinoid use.

BOX 12-3 **Summary of Chapter Conclusions***

There is substantial evidence of a statistical association between cannabis use and:

- The development of schizophrenia or other psychoses, with the highest risk among the most frequent users (12-1)

There is moderate evidence of a statistical association between cannabis use and:

- Better cognitive performance among individuals with psychotic disorders and a history of cannabis use (12-2a)
- Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use) (12-4)
- A small increased risk for the development of depressive disorders (12-5)
- Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users (12-7a)
- Increased incidence of suicide completion (12-7b)
- Increased incidence of social anxiety disorder (regular cannabis use) (12-8b)

There is moderate evidence of *no* statistical association between cannabis use and:

- Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders (12-2c)

There is limited evidence of a statistical association between cannabis use and:

- An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders (12-2b)
- The likelihood of developing bipolar disorder, particularly among regular or daily users (12-3)
- The development of any type of anxiety disorder, except social anxiety disorder (12-8a)
- Increased symptoms of anxiety (near daily cannabis use) (12-9)
- Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (12-11)

There is no evidence to support or refute a statistical association between cannabis use and:

- Changes in the course or symptoms of depressive disorders (12-6)
- The development of posttraumatic stress disorder (12-10)

* Numbers in parentheses correspond to chapter conclusion numbers.

REFERENCES

- ADAA (Anxiety and Depression Association of America). 2016. Depression. <https://www.adaa.org/understanding-anxiety/depression> (accessed November 17, 2016).
- APA (American Psychiatric Association). 2013. *Diagnostic and statistical manual of mental disorders, 5th ed.* Arlington, VA: American Psychiatric Publishing.
- Auther, A. M., K. S. Cadenhead, R. E. Carrion, J. Addington, C. E. Bearden, T. D. Cannon, T. H. McGlashan, D. O. Perkins, L. Seidman, M. Tsuang, E. F. Walker, S. W. Woods, and B. A. Cornblatt. 2015. Alcohol confounds relationship between cannabis misuse and psychosis conversion in a high-risk sample. *Acta Psychiatrica Scandinavica* 132(1):60–68.
- Azofeifa, A., M. E. Mattson, G. Schauer, T. McAfee, A. Grant, and R. Lyerla. 2016. National estimates of marijuana use and related indicators—National Survey on Drug Use and Health, United States, 2002–2014. *Morbidity and Mortality Weekly Report* 65(SS-11):1–25.
- Barrowclough, C., R. Emsley, E. Eisner, R. Beardmore, and T. Wykes. 2013. Does change in cannabis use in established psychosis affect clinical outcome? *Schizophrenia Bulletin* 39(2):339–348.
- Barrowclough, C., L. Gregg, F. Lobban, S. Bucci, and R. Emsley. 2015. The impact of cannabis use on clinical outcomes in recent onset psychosis. *Schizophrenia Bulletin* 41(2):382–390.
- Bechtold, J., T. Simpson, H. R. White, and D. Pardini. 2015. Chronic adolescent marijuana use as a risk factor for physical and mental health problems in young adult men. *Psychology of Addictive Behaviors* 29(3):552–563.
- Blanco, C., D. S. Hasin, M. M. Wall, L. Florez-Salamanca, N. Hoertel, S. Wang, B. T. Kerridge, and M. Olfson. 2016. Cannabis use and risk of psychiatric disorders: Prospective evidence from a U.S. national longitudinal study. *JAMA Psychiatry* 73(4):388–395.
- Borges, G., C. L. Bagge, and R. Orozco. 2016. A literature review and meta-analyses of cannabis use and suicidality. *Journal of Affective Disorders* 195:63–74.
- Brook, J. S., J. Y. Lee, E. Rubenstone, D. W. Brook, and S. J. Finch. 2014. Triple comorbid trajectories of tobacco, alcohol, and marijuana use as predictors of antisocial personality disorder and generalized anxiety disorder among urban adults. *American Journal of Public Health* 104(8):1413–1420.
- Brook, J. S., C. Zhang, E. Rubenstone, B. A. Primack, and D. W. Brook. 2016. Comorbid trajectories of substance use as predictors of antisocial personality disorder, major depressive episode, and generalized anxiety disorder. *Addictive Behaviors* 62:114–121.
- Brugha, T. S., R. Matthews, Z. Morgan, T. Hill, J. Alonso, and D. R. Jones. 2012. Methodology and reporting of systematic reviews and meta-analyses of observational studies in psychiatric epidemiology: Systematic review. *British Journal of Psychiatry* 200(6):446–453.
- CBHSQ (Center for Behavioral Health Statistics and Quality). 2015. *Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health* (HHS Publication No. SMA 15-4927, NSDUH Series H-50). <http://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf> (accessed December 5, 2016).
- CDC (Centers for Disease Control and Prevention). 2014. *Injury Prevention and Control. Fatal Injury Reports*. https://www.cdc.gov/injury/wisqars/fatal_injury_reports.html (accessed December 15, 2016).
- Colizzi, M., C. Iyegbe, J. Powell, G. Ursini, A. Porcelli, A. Bonvino, P. Taurisano, R. Romano, R. Masellis, G. Blasi, C. Morgan, K. Aitchison, V. Mondelli, S. Luzi, A. Kolliakou, A. David, R. M. Murray, A. Bertolino, and M. Di Forti. 2015. Interaction between functional genetic variation of DRD2 and cannabis use on risk of psychosis. *Schizophrenia Bulletin* 41(5):1171–1182.

- Cougle, J. R., J. K. Hakes, R. J. Macatee, J. Chavarria, and M. J. Zvolensky. 2015. Quality of life and risk of psychiatric disorders among regular users of alcohol, nicotine, and cannabis: An analysis of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). *Journal of Psychiatric Research* 66-67:135–141.
- Crane, N. A., S. A. Langenecker, and R. J. Mermelstein. 2015. Gender differences in the associations among marijuana use, cigarette use, and symptoms of depression during adolescence and young adulthood. *Addictive Behaviors* 49:33–39.
- Di Forti, M., A. Marconi, E. Carra, S. Fraietta, A. Trotta, M. Bonomo, F. Bianconi, P. Gardner-Sood, J. O'Connor, M. Russo, S. A. Stilo, T. R. Marques, V. Mondelli, P. Dazzan, C. Pariante, A. S. David, F. Gaughran, Z. Atakan, C. Iyegbe, J. Powell, C. Morgan, M. Lynskey, and R. M. Murray. 2015. Proportion of patients in South London with first-episode psychosis attributable to use of high potency cannabis: A case-control study. *The Lancet Psychiatry* 2(3):233–238.
- Donoghue, K., and G. A. Doody. 2012. Effect of illegal substance use on cognitive function in individuals with a psychotic disorder: A review and meta-analysis. *Neuropsychology* 26(6):785–801.
- Dubertret, C., I. Bidard, J. Ades, and P. Gorwood. 2006. Lifetime positive symptoms in patients with schizophrenia and cannabis abuse are partially explained by co-morbid addiction. *Schizophrenia Research* 86(1-3):284–290.
- EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). 2016. Comorbidity of substance use and mental health disorders in Europe. Perspectives on Drugs. http://www.emcdda.europa.eu/system/files/attachments/2639/Comorbidity_POD2016.pdf (accessed November 24, 2016).
- Feingold, D., M. Weiser, J. Rehm, and S. Lev-Ran. 2014. The association between cannabis use and mood disorders: A longitudinal study. *Journal of Affective Disorders* 172:211–218.
- Feingold, D., M. Weiser, J. Rehm, and S. Lev-Ran. 2016. The association between cannabis use and anxiety disorders: Results from a population-based representative sample. *European Neuropsychopharmacology* 26(3):493–505.
- Gage, S. H., M. Hickman, J. Heron, M. R. Munafo, G. Lewis, J. Macleod, and S. Zammit. 2015. Associations of cannabis and cigarette use with depression and anxiety at age 18: Findings from the Avon Longitudinal Study of Parents and Children. *PLOS ONE* 10(4): e0122896.
- Gentes, E. L., A. R. Schry, T. A. Hicks, C. P. Clancy, C. F. Collie, A. C. Kirby, M. F. Dennis, M. A. Hertzberg, J. C. Beckham, and P. S. Calhoun. 2016. Prevalence and correlates of cannabis use in an outpatient VA posttraumatic stress disorder clinic. *Psychology of Addictive Behaviors* 30(3):415–421.
- Gibbs, M., C. Winsper, S. Marwaha, E. Gilbert, M. Broome, and S. P. Singh. 2015. Cannabis use and mania symptoms: A systematic review and meta-analysis. *Journal of Affective Disorders* 171:39–47.
- Grunberg, V. A., K. A. Cordova, L. C. Bidwell, and T. A. Ito. 2015. Can marijuana make it better? Prospective effects of marijuana and temperament on risk for anxiety and depression. *Psychology of Addictive Behaviors* 29(3):590–602.
- Horwood, L. J., D. M. Fergusson, C. Coffey, G. C. Patton, R. Tait, D. Smart, P. Letcher, E. Silins, and D. M. Hutchinson. 2012. Cannabis and depression: An integrative data analysis of four Australasian cohorts. *Drug and Alcohol Dependence* 126(3):369–378.
- Johnson, M. J., J. D. Pierce, S. Mavandadi, J. Klaus, D. Defelice, E. Ingram, and D. W. Oslin. 2016. Mental health symptom severity in cannabis using and non-using veterans with probable PTSD. *Journal of Affective Disorders* 190:439–442.
- Kedzior, K. K., and L. T. Laeber. 2014. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population—A meta-analysis of 31 studies. *BMC Psychiatry* 14:136.

- Kirkbride, J. B., A. Errazuriz, T. J. Croudace, C. Morgan, D. Jackson, J. Boydell, R. M. Murray, and P. B. Jones. 2012. Incidence of schizophrenia and other psychoses in England, 1950–2009: A systematic review and meta-analyses. *PLOS ONE* 7(3):e31660.
- Large, M., S. Sharma, M. T. Compton, T. Slade, and O. Nielssen. 2011. Cannabis use and earlier onset of psychosis: A systematic meta-analysis. *Archives of General Psychiatry* 68(6):555–561.
- Lev-Ran, S., B. Le Foll, K. McKenzie, T. P. George, and J. Rehm. 2013. Bipolar disorder and co-occurring cannabis use disorders: Characteristics, co-morbidities and clinical correlates. *Psychiatry Research* 209(3):459–465.
- Mallen, C., G. Peat, and P. Croft. 2006. Quality assessment of observational studies is not commonplace in systematic reviews. *Journal of Clinical Epidemiology* 59(8):765–769.
- Manhapra, A., E. Stefanovics, and R. Rosenheck. 2015. Treatment outcomes for veterans with PTSD and substance use: Impact of specific substances and achievement of abstinence. *Drug and Alcohol Dependence* 156:70–77.
- Marconi, A., M. Di Forti, C. M. Lewis, R. M. Murray, and E. Vassos. 2016. Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia Bulletin* 42(5):1262–1269.
- McLoughlin, B. C., J. A. Pushpa-Rajah, D. Gillies, J. Rathbone, H. Variend, E. Kalakouti, and K. Kyprianou. 2014. Cannabis and schizophrenia. *Cochrane Database of Systematic Reviews* 10:CD004837.
- MedlinePlus. 2016. Suicide. <https://medlineplus.gov/suicide.html> (accessed October 26, 2016).
- Moore, T. H., S. Zammit, A. Lingford-Hughes, T. R. Barnes, P. B. Jones, M. Burke, and G. Lewis. 2007. Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet* 370(9584):319–328.
- Myles, N., H. Newall, O. Nielssen, and M. Large. 2012. The association between cannabis use and earlier age at onset of schizophrenia and other psychoses: Meta-analysis of possible confounding factors. *Current Pharmaceutical Design* 18(32):5055–5069.
- NIDA (National Institute on Drug Abuse). 2011. DrugFacts—comorbidity: Addiction and other mental disorders. <https://www.drugabuse.gov/publications/drugfacts/comorbidity-addiction-other-mental-disorders> (accessed November 24, 2016).
- NIDA. 2015. Research reports: Marijuana. https://www.drugabuse.gov/sites/default/files/mjrrs_4_15.pdf (accessed November 29, 2016).
- NIMH (National Institute of Mental Health). 2015. Schizophrenia. <https://www.nimh.nih.gov/health/publications/schizophrenia-booklet-12-2015/index.shtml> (accessed October 28, 2016).
- NIMH. 2016. Bipolar disorder. <https://www.nimh.nih.gov/health/topics/bipolar-disorder/index.shtml> (accessed October 25, 2016).
- NIMH. n.d. Any anxiety disorder among adults. <https://www.nimh.nih.gov/health/statistics/prevalence/any-anxiety-disorder-among-adults.shtml> (accessed October 26, 2016).
- Nkansah-Amankra, S., and M. Minelli. 2016. “Gateway hypothesis” and early drug use: Additional findings from tracking a population-based sample of adolescents to adulthood. *Preventive Medicine Reports* 4:134–141.
- Power, B. D., M. Dragovic, J. C. Badcock, V. A. Morgan, D. Castle, A. Jablensky, and N. C. Stefanis. 2015. No addictive effect of cannabis on cognition in schizophrenia. *Schizophrenia Research* 168(1-2):245–251.
- Rabin, R. A., K. K. Zakzanis, and T. P. George. 2011. The effects of cannabis use on neurocognition in schizophrenia: A meta-analysis. *Schizophrenia Research* 128(1-3):111–116.
- Rasic, D., S. Weerasinghe, M. Asbridge, and D. B. Langille. 2013. Longitudinal associations of cannabis and illicit drug use with depression, suicidal ideation and suicidal attempts among Nova Scotia high school students. *Drug and Alcohol Dependence* 129(1-2):49–53.

- Rehman, I. U., and S. Farooq, S. 2007. Cannabis abuse in patients with schizophrenia: Pattern and effects on symptomatology. *Journal of the College of Physicians and Surgeons, Pakistan* 17(3):158–161.
- SAMHSA (Substance Abuse and Mental Health Services Administration). 2015. *Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health*. <http://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf> (accessed November 24, 2016).
- Sanchez-Torres, A. M., V. Basterra, A. Rosa, L. Fananas, A. Zarzuela, B. Ibanez, V. Peralta, and M. J. Cuesta. 2013. Lifetime cannabis use and cognition in patients with schizophrenia spectrum disorders and their unaffected siblings. *European Archives of Psychiatry and Clinical Neuroscience* 263(8):643–653.
- Schnell, T., D. Koethe, J. Daumann, and E. Gouzoulis-Mayfrank. 2009. The role of cannabis in cognitive functioning of patients with schizophrenia. *Psychopharmacology* 205(1):45–52.
- Seddon, J. L., M. Birchwood, A. Copello, L. Everard, P. B. Jones, D. Fowler, T. Amos, N. Freemantle, V. Sharma, M. Marshall, and S. P. Singh. 2016. Cannabis use is associated with increased psychotic symptoms and poorer psychosocial functioning in first-episode psychosis: A report from the UK National Eden Study. *Schizophrenia Bulletin* 42(3):619–625.
- Shalit, N., G. Shoval, D. Shlosberg, D. Feingold, and S. Lev-Ran. 2016. The association between cannabis use and suicidality among men and women: A population-based longitudinal study. *Journal of Affective Disorders* 205:216–224.
- Silins, E., L. J. Horwood, G. C. Patton, D. M. Fergusson, C. A. Olsson, D. M. Hutchinson, E. Spry, J. W. Toumbourou, L. Degenhardt, W. Swift, C. Coffey, R. J. Tait, P. Letcher, J. Copeland, R. P. Mattick, S. Allsop, W. Hall, R. Hayatbakhsh, K. Little, J. Najman, R. Skinner, and T. Slade. 2014. Young adult sequelae of adolescent cannabis use: An integrative analysis. *The Lancet Psychiatry* 1(4):286–293.
- Szoke, A., A. M. Galliot, J. R. Richard, A. Ferchiou, G. Baudin, M. Leboyer, and F. Schurhoff. 2014. Association between cannabis use and schizotypal dimensions—A meta-analysis of cross-sectional studies. *Psychiatry Research* 219(1):58–66.
- Tosato, S., A. Lasalvia, C. Bonetto, R. Mazzoncini, D. Cristofalo, K. De Santi, M. Bertani, S. Bissoli, L. Lazzarotto, G. Marrella, D. Lamonaca, R. Riolo, F. Gardellin, A. Urbani, M. Tansella, and M. Ruggeri. 2013. The impact of cannabis use on age of onset and clinical characteristics in first-episode psychotic patients. Data from the Psychosis Incident Cohort Outcome Study (PICOS). *Journal of Psychiatric Research* 47(4):438–444.
- Valmaggia, L. R., F. L. Day, C. Jones, S. Bissoli, C. Pugh, D. Hall, S. Bhattacharyya, O. Howes, J. Stone, P. Fusar-Poli, M. Byrne, and P. K. McGuire. 2014. Cannabis use and transition to psychosis in people at ultra-high risk. *Psychological Medicine* 44(12):2503–2512.
- van der Meer, F. J., E. Velthorst, C. J. Meijer, M. W. Machielsen, and L. de Haan. 2012. Cannabis use in patients at clinical high risk of psychosis: Impact on prodromal symptoms and transition to psychosis. *Current Pharmaceutical Design* 18(32):5036–5044.
- van Dijk, D., M. W. J. Koeter, R. Hijman, R. S. Kahn, and W. van den Brink. 2012. Effect of cannabis use on the course of schizophrenia in male patients: A prospective cohort study. *Schizophrenia Research* 137(1–3):50–57.
- van Winkel, R., N. J. van Beveren, and C. Simons. 2011. AKT1 moderation of cannabis-induced cognitive alterations in psychotic disorder. *Neuropsychopharmacology* 36(12):2529–2537.
- Villagonzalo, K. A., S. Dodd, F. Ng, S. Mihaly, A. Langbein, and M. Berk. 2011. The relationship between substance use and posttraumatic stress disorder in a methadone maintenance treatment program. *Comprehensive Psychiatry* 52(5):562–566.
- Wilkinson, S. T., E. Stefanovics, and R. A. Rosenheck. 2015. Marijuana use is associated with worse outcomes in symptom severity and violent behavior in patients with posttraumatic stress disorder. *Journal of Clinical Psychiatry* 76(9):1174–1180.

- Wilkinson, A. L., C. T. Halpern, and A. H. Herring. 2016. Directions of the relationship between substance use and depressive symptoms from adolescence to young adulthood. *Addictive Behaviors* 60:64–70.
- Yucel, M., E. Bora, D. I. Lubman, N. Solowij, W. J. Brewer, S. M. Cotton, P. Conus, M. J. Takagi, A. Fornito, S. J. Wood, P. D. McGorry, and C. Pantelis. 2012. The impact of cannabis use on cognitive functioning in patients with schizophrenia: A meta-analysis of existing findings and new data in a first-episode sample. *Schizophrenia Bulletin* 38(2):316–330.
- Zammit, S., T. H. Moore, A. Lingford-Hughes, T. R. Barnes, P. B. Jones, M., Burke, and G. Lewis. 2008. Effects of cannabis use on outcomes of psychotic disorders: Systematic review. *British Journal of Psychiatry* 193(5):357–363.
- Zorrilla, I., J. Aguado, J. M. Haro, S. Barbeito, S. Lopez Zurbano, A. Ortiz, P. Lopez, and A. Gonzalez-Pinto. 2015. Cannabis and bipolar disorder: Does quitting cannabis use during manic/mixed episode improve clinical/functional outcomes? *Acta Psychiatrica Scandinavica* 131(2):100–110.

13

Problem Cannabis Use

Chapter Highlights

- Greater frequency of cannabis use increases the likelihood of developing problem cannabis use.
- Initiating cannabis use at a younger age increases the likelihood of developing problem cannabis use.

A recent national survey reported that 22.2 million Americans (ages 12 or older) identify as current users of cannabis (CBHSQ, 2015). A subgroup of these users, 4.2 million Americans, reported experiencing symptoms in the previous year that would qualify them for cannabis use disorder (CUD) (CBHSQ, 2015). Unfortunately, the literature remains unclear on the association or developmental link between varying levels of cannabis use and the development of “problem” cannabis use or cannabis use disorder, particularly at different age groups (e.g., 12 years or older).

In this chapter, the committee reviews the current research evidence that most directly addresses prioritized research questions related to the association between cannabis use and the development of problem cannabis use and to the risk and protective factors involved in the development or exacerbation of problem use. An initial search of the primary literature (see Appendix B) produced a substantial number of primary articles for the committee to review. Due to the time constraints of the study, additional search constraints were added to zero in on the types of studies

that would likely produce the clearest research conclusions. For example, literature searches were limited to articles that included the following search terms: longitudinal, prospective, and case-control. The primary literature was further limited to studies that included a sample size of >500 participants and to studies that investigated problem cannabis use as a function of the most relevant risk factors, including mental health, the age of initiation of cannabis use, risk factors during adolescence, biological sex, and other drug use. Large population-based studies that explored multiple demographic variables were also included.

It is of note, however, that due to the specific search restrictions outlined above, controlled laboratory studies with cannabis were not included in the committee's set of articles to review. There do, in fact, exist controlled lab studies that assess the direct effects of cannabis on behaviors relevant to cannabis use disorder and the dose-dependent effects of cannabis and that are related to its abuse liability. Unfortunately, because of the constraints of this study, these findings are not incorporated in the chapter's discussion. Furthermore, the committee's prioritized research questions did not examine the association between low-level cannabis use or infrequent cannabis use and the development of problem cannabis use.

To inform their research conclusions, the committee reviewed two of the most recent good- to fair-quality systematic reviews and 26 primary literature articles.

PROBLEM CANNABIS USE

As noted above, the literature is unclear on the association between cannabis use and the progression to the sort of cannabis use determined to be "problem" use. A major contributor to this issue is the lack of official distinction between "risky" or "problem" use of cannabis (Casajuana et al., 2016). In recent years, CUD¹ has been termed an official psychiatric disorder (APA, 2013; WHO, 2015). A current *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V) diagnosis of CUD replaces the previous diagnoses of cannabis abuse and cannabis dependence. Although some progress has been made in standardizing terminology, explicit characterizations of cannabis use patterns that *precede* abuse or dependence still remain unclear (Casajuana et al., 2016). Given this context, for the purposes of this chapter the committee will use the broad term "problem cannabis use disorder" to encompass various levels of

¹ In brief, CUD is a diagnosable psychiatric disorder defined as a problematic pattern of cannabis use leading to clinically significant personal, social, physical, and/or psychological distress or impairment.

hazardous or potentially harmful cannabis use patterns, including those related to CUD, dependence, and abuse.

Which Characteristics of Cannabis Use Are Associated with the Progression to Developing Problem Cannabis Use?

Systematic Reviews

The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and cannabis use disorder, dependence, abuse, or problem cannabis use.

Primary Literature

Several studies using large population-based surveys have explored the rates of cannabis use disorder and the variables that affect progression from the initiation of use to problem cannabis use. According to findings from Wave 1 (baseline; 2001–2002) and Wave 2 (follow-up; 2004–2005) of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a survey of a nationally representative sample of U.S. adults ages 18 years and older ($n = 34,653$ in Wave 2), cannabis use reported during the first wave was significantly associated with any cannabis use disorder during the second wave (adjusted odds ratio [aOR], 9.5; 95% confidence interval [CI] = 6.4–14.1); 14.1 percent of past-year cannabis users in Wave 1 met the criteria for cannabis abuse in Wave 2, and 5.1 percent met criteria for dependence, as compared with 0.7 percent of participants who reported no past-year cannabis use during Wave 1 who met the criteria for cannabis abuse and 0.2 percent who met the criteria for cannabis dependence (Blanco et al., 2016). This study accounted for multiple sociodemographic factors that may have affected the outcome.

The progression of cannabis use to developing cannabis use disorder as a function of the frequency of cannabis use was also explored using Waves 1 and 2 of the NESARC data (Cogle et al., 2016). Among the past-year weekly nondependent cannabis users in Wave 1 ($n = 435$), 9.7 percent progressed to cannabis dependence in Wave 2; however, an increased frequency of cannabis use per day only weakly predicted progression of cannabis use to CUD (odds ratio [OR], 1.08; CI = 1.04–1.13) in a prospective analysis. A cross-sectional analysis of Wave 1 data found that 8.0 percent of respondents who reported using cannabis at least once in the past year met the criteria for dependence, whereas among weekly and daily cannabis smokers, 17.0 percent and 18.8 percent, respectively, met the criteria for dependence.

Using data obtained from the U.S. National Household Survey on

Drug Abuse (NHSDA) conducted in 2001 with a representative sample of U.S. residents 12 years of age and older ($n = 114,241$), Chen and colleagues (2005) explored the rates of developing cannabis dependence syndrome after onset of use. Of the recent onset users (individuals that used cannabis within 24 months prior to assessment), an estimated 3.9 percent developed dependence during the interval since first use (median time = 1 year). Of those who initiated cannabis use more than 24 months before the assessment, and were also active cannabis users within the past year, 9.9 percent developed dependence (Chen et al., 2005).

Using data from two large U.S. surveys—the 1991 National Longitudinal Alcohol Epidemiologic Survey (NLAES) ($n = 42,862$) and the 2002 NESARC ($n = 43,093$)—Compton and colleagues (2004) assessed the rates of cannabis use disorder as a function of biological sex, ethnicity, and frequency of cannabis use. They found that the overall prevalence of DSM-IV cannabis abuse and dependence increased significantly from 1.2 percent to 1.5 percent between 1991 and 2001. The greatest increases in these rates were observed among young black men and women ($p < 0.001$), and young Hispanic men ($p = 0.006$). The increase in the rates of cannabis use disorder among cannabis users was observed in the absence of self-reported increases in frequency or quantity of use ($p = 0.002$); this suggests that the increases in cannabis use disorders may be due to the increased potency (percent tetrahydrocannabinol [THC]) of cannabis between 1991 and 2001.

Discussion of Findings

The limitations of these studies include the reliance on self-reported cannabis use, the fact that data were restricted to two time points of assessment separated by 3 years, and that the findings are based on epidemiological data obtained more than 10 years ago. A significant issue with relying on self-report methodologies to ascertain problem cannabis use is that this requires that the respondent have insight into the fact that cannabis is actually causing problems in order to meet criteria for cannabis abuse/dependence (as per the DSM-IV) or CUD (as per the DSM-V). Furthermore, while the primary literature indicates a weak association between the frequency of use and a greater risk of developing cannabis use disorder, it should be noted that the frequency of use in these studies was assessed in the absence of determining the amount of cannabis used per occasion, which is a primary variable hypothesized to affect the rates of developing problem cannabis use.

Cannabis use is increasing across the country and across age groups (Hasin et al., 2015); the strength of cannabis has increased (ElSohly et al., 2016); and different routes of cannabis administration have become popu-

lar, including vaping, dabs, and edibles (Daniulaityte et al., 2015; Kilmer et al., 2013; Pacula et al., 2016). These trends may reflect an increased vulnerability to developing problem cannabis use relative to what was estimated based on the Wave 1 and Wave 2 NESARC data collected in 2001–2001 and 2004–2005. Therefore, the estimated risk of developing problem cannabis use based on these data may not accurately reflect the risk now, given the current trends.

CONCLUSION 13-1 There is substantial evidence for a statistical association between increases in cannabis use frequency and the progression to developing problem cannabis use.

Are There Risk and Protective Factors for Developing Problem Cannabis Use?

Anxiety

Systematic Reviews Kedzior and Laeber (2014) searched two large databases for articles published from inception through 2013 to identify studies of cannabis use and anxiety. They included cross-sectional and longitudinal studies conducted in noninstitutionalized populations, with anxiety diagnoses based on DSM or *International Classification of Diseases* (ICD) criteria, odds ratios, or data sufficient for the calculation of a measure of effects, and they included comparison data from healthy nonusers. Their purpose was to examine both of the possible temporal relationships between cannabis use and anxiety (i.e., the effect of anxiety on cannabis use and the effect of cannabis use on anxiety). They identified 31 studies for their review. Five of these examined cannabis use at baseline and anxiety at follow-up, and the remainder considered the role of anxiety as a risk factor for cannabis use. Sample sizes were almost 2,000 or greater in four studies and more than 12,000 in a fifth study. After analyzing various subsets of the selected articles, the authors concluded that there was a small positive association between anxiety and CUD (OR, 1.68; 95% CI = 1.23–2.31, $n = 13$ studies). One study included in the analysis assessed anxiety at baseline and cannabis use at follow-up and did not find an association (OR, 0.94; 95% CI = 0.86–1.03), but it did not report on problem cannabis use at follow-up. The authors found little evidence of publication bias after their assessment, and they reported a moderate-high heterogeneity. They offered three possible explanations of this heterogeneity: differences in adjustment for confounding when calculating the OR, year of publication, and different methods for diagnosing anxiety. Based on this systematic review, it appears that while there is a small association between anxiety and CUD, anxiety does not seem to be a predisposing risk factor for developing CUD.

Primary Literature The committee did not identify any good-quality primary literature that reported on anxiety as a risk or a protective factor for developing problem cannabis use and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Stimulant Medication in Children Diagnosed with Attention Deficit Hyperactivity Disorder

Systematic Reviews Humphreys et al. (2013) conducted a systematic literature review and meta-analysis to assess the association between childhood treatment with stimulant medication and later substance use, abuse, or dependence. They searched the literature published between 1980 and 2012 and included published and unpublished studies with a longitudinal design, binary measures to identify children with attention deficit hyperactivity disorder (ADHD), binary substance use and abuse measures, and data allowing the calculation of odds ratios. Fifteen studies were included in the review; nine of these evaluated the association of stimulant medication with a lifetime history of ever using marijuana, and nine evaluated the association of stimulant medication with cannabis abuse or dependence. All study subjects were children at the time of enrollment, and the follow-up time ranged from 4 to 28 years in the group of 9 studies reviewed, with the mean age at follow-up ranging from 15 to 26 years. One of the studies in this systematic review included children as young as 4 years of age who would not be expected to develop CUD in the follow-up time period. The percentage of study subjects who were male ranged from 0 to 100, with the majority of the studies being more than 80 percent male. The researchers reported an OR of 1.01 (95% CI = 0.68–1.50) for the association between stimulant medication and marijuana abuse or dependence. Some suggestion of publication bias was noted, and heterogeneity was noted in the group of nine studies with data about marijuana abuse or dependence. These results suggest that medication for ADHD during childhood does not constitute a risk factor for developing problem cannabis use later in life.

Primary Literature The committee did not identify any good-quality primary literature that reported stimulant medication in children diagnosed with ADHD as a risk or a protective factor for developing problem cannabis use and that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Psychopathology

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on psychopathology as a risk or a protective factor for developing problem cannabis use.

Primary Literature Data obtained from the 2001 and 2005 NESARC, a survey of a nationally representative sample of U.S. adults ages 18 years and older ($n = 34,653$ in Wave 2), explored anxiety as a risk factor for progression to cannabis use disorder. Using data from Wave 2 (comprised of 34,653 participants from Wave 1), Feingold and colleagues (2016) found that anxiety disorders were not associated with an increased incidence of cannabis use disorders (aOR, 0.68; 95% CI = 0.41–1.14). Similarly, a prospective analysis using Wave 1 and Wave 2 NESARC data also found that anxiety disorders failed to predict progression from cannabis use to cannabis dependence in weekly cannabis users (Cougler et al., 2016).

Another analysis used these data to determine the association between baseline major depressive disorder (MDD) as a risk factor for cannabis use disorders (Pacek et al., 2013). A positive relationship was observed between baseline MDD and cannabis use disorders (OR, 2.01, 95% CI = 1.09–3.68); baseline MDD also increased the risk of co-occurring alcohol and cannabis use disorders (OR, 5.23; 95% CI = 1.28–21.34) when compared to individuals without baseline MDD. When adjusting the model to account for potential confounding variables, the association between baseline MDD and the development of cannabis use disorders alone, and co-occurring with alcohol use disorders was retained (aOR, 2.28; 95% CI = 1.28–4.05 for cannabis use disorders alone and aOR, 4.51, 95% CI = 1.31–15.60 for comorbid alcohol and cannabis use disorders). These findings support a strong association between MDD and the development of cannabis use disorders. According to a later prospective analysis (Cougler et al., 2016), among weekly, nondependent cannabis users in Wave 1, depressive disorders did not significantly predict progression to cannabis dependence in Wave 2 (OR, 0.89; 95% CI = 0.58–1.38) (Cougler et al., 2016). The discrepancy between these two findings may be due to the former study assessing respondents who met the criteria for MDD. Also, the pool of respondents in the earlier study was not limited to those who reported weekly cannabis use during Wave 1, as was the case with the later study.

Another study assessing the impact of baseline depressive symptoms on developing cannabis abuse used data from a longitudinal study involving 1,980 participants (the 1980 Baltimore Epidemiologic Catchment Area study). In this study, a subset of participants ($n = 1,837$) were assessed for cannabis use disorders 14 to 16 years after initial assessment (Bovasso, 2001). Depressive symptoms failed to predict cannabis abuse at follow-up assessments, which indicated that among the population

studied, depression was not a risk factor for later cannabis abuse. The long duration between the initial assessment and the follow-up and the presence of significant attrition were significant limitations to this study.

In order to determine the effects of psychotic disorders on the risk for heavy cannabis use, data obtained from the Genomic Psychiatric Cohort—a clinically assessed multiethnic sample of participants ($n = 9,142$) with a diagnosis of schizophrenia, bipolar disorder with psychotic features, or schizoaffective disorders—were compared to a control population ($n = 10,195$) (Hartz et al., 2014). Relative to the control population, individuals with chronic psychotic disorders were found to have an increased risk for heavy cannabis use, defined by the researchers as cannabis use more than 21 times per year (OR, 3.5; 95% CI = 3.2–3.7). It is important to note, however, that it remains difficult to determine how heavy cannabis use translates to problem cannabis use, cannabis dependence, or CUD.

A prospective analysis using data from Waves 1 and 2 of the NESARC found that personality disorders failed to predict a progression from past-year, weekly nondependent cannabis use in Wave 1 to cannabis dependence in Wave 2 (OR, 0.91; 95% CI = 0.62–1.34). This same analysis demonstrated that bipolar disorder was associated with a lower risk for developing CUD (OR, 0.43; 95% CI = 0.36–0.52) (Cogle et al., 2016).

Biological Sex

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on biological sex as a risk or a protective factor for developing problem cannabis use.

Primary Literature Data from the NLAES ($n = 42,862$) were analyzed in effort to determine the effect of biological sex on the risk of developing cannabis use disorders (Grant et al., 2006). Of the participants that reported cannabis use at least 12 times, women were less likely to be categorized with cannabis “abuse/moderate dependence” relative to men (8 percent versus 14 percent) or “severe abuse/dependence” (3 percent versus 6 percent). While men were consistently more likely to report hazardous cannabis use relative to women, women were more likely to report withdrawal and to have higher rates of four symptoms of dependence (i.e., emotional problems, giving up activities, using more cannabis than intended, withdrawal) in the “abuse/moderate dependence” category than men. These findings may suggest either that men and women differ in cannabis dependence symptomatology or that they differ in their willingness to self-report the symptoms.

Using data obtained from Wave IV of the National Longitudinal Study of Adolescent Health—a nationally representative population-

based survey of young adults ages 24 to 32 ($n = 15,500$; interviewed from 2008–2009)—lifetime prevalence rates of cannabis dependence were determined to be 8.3 percent, and they were higher among males than among females (Haberstick et al., 2014). However, a prospective analysis using data from Wave 1 and Wave 2 of the NESARC failed to find that biological sex predicted a progression from cannabis use to cannabis dependence in weekly nondependent cannabis users (OR, 1.17; 95% CI = 0.75–1.81) (Cogle et al., 2016).

Progression from the onset of cannabis use to the development of cannabis dependence as a function of biological sex was explored using data obtained from the NHSDA, which was conducted in 2001 with a representative sample of U.S. residents 12 years of age and older ($n = 114,241$) (Chen et al., 2005). The rate for developing cannabis dependence 24 months after onset of use was 3.9 percent for both men and women. However, it is not known if differences between men and women would have emerged if a shorter time frame from cannabis use onset had been explored.

Other Drug Use

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on other drug use as a risk or a protective factor for developing problem cannabis use.

Primary Literature To explore the impact of other drug use as a risk factor for developing problem cannabis use, data obtained from the NHSDA conducted in 2001 with a representative sample of U.S. residents 12 years of age and older ($n = 114,241$) were analyzed. The rate of developing cannabis dependence within 24 months of first cannabis use was doubled among respondents who had experience with three or more other drugs (tobacco, alcohol, and other drugs) prior to cannabis use (adjusted risk ratio [aRR] = 2.2; 95% CI = 1.1–4.3; $p = 0.03$) (Chen et al., 2005). However, a prospective analysis using data from Waves 1 and 2 of the NESARC failed to find that alcohol or nicotine dependence predicted progression from cannabis use to cannabis dependence (OR, 0.88; 95% CI = 0.58–1.32 and OR, 0.77; 95% CI = 0.52–1.13, respectively) (Cogle et al., 2016).

Age—Older Population

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on older age as a risk or a protective factor for developing problem cannabis use.

Primary Literature Based on the large population-based U.S. National Survey on Drug Use and Health, the prevalence of cannabis use in the United States was assessed in a population more than 50 years of age ($n = 10,953$; data from 2005 and 2006). Only 0.12 percent of the population met the criteria for cannabis abuse and dependence demonstrating that, at the time of this survey, this is an age group that is at low risk for developing CUD (Blazer and Wu, 2009).

Age of Initiation of Cannabis Use

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the age of initiation of cannabis use as a risk or a protective factor for developing problem cannabis use.

Primary Literature The age of initiation of cannabis use as a risk factor for developing cannabis dependence has been explored in many studies. Chen et al. (2005) used data obtained from the NHSDA conducted in 2001 with a representative sample of U.S. residents 12 years of age and older ($n = 114,241$). Adolescent onset cannabis users were more likely to become dependent than respondents who had initiated cannabis use during adulthood. Using data obtained from adult onset users of cannabis (21 years of age and older) as a reference, Chen and colleagues found a strong association between an onset of cannabis use between 11 and 13 years of age and the relative risk of becoming dependent (aRR = 10.8; 95% CI = 2.5–47.1). The estimated risk ratio of developing cannabis dependence when initiating cannabis use at 14 to 15 years of age was 12.0 (95% CI = 2.9–50.3).

Another study exploring early, frequent cannabis use as a risk factor for developing cannabis use disorder used data from three long-running surveys in Australia and New Zealand² (Silins et al., 2014). Compared to individuals who had never used cannabis, those who were daily users before 17 years of age had significantly greater odds of later developing cannabis dependence ($n = 2,675$; aOR, 17.95; 95% CI = 9.44–34.12). This study controlled for 53 covariates, including socio-demographic factors and other potential antecedents to the development of problem cannabis use that may have affected the findings.

A longitudinal study of a community-based sample of adolescents and young adults surveyed between 14 and 24 years of age in Munich, Germany, with four waves of assessments over a 10-year period ($n = 3,021$ at baseline) ascertained the prevalence rates of DSM-IV cannabis

² These surveys include the Australian Temperament Project, the Christchurch Health and Development Study, and the Victorian Adolescent Health Cohort Study.

dependence as a function of cannabis use (Perkonigg et al., 2008). During the first assessment (at baseline), 1.5 percent of the sample met the criteria for DSM-IV cannabis dependence. Among those who reported using cannabis at that time, 4.3 percent met the criteria for dependence. At the 10-year follow-up, 6.1 percent of those who reported using cannabis at baseline met the criteria for dependence. The authors concluded that the higher rates of cannabis dependence during the 10-year follow-up assessment suggested that cannabis use early in life may be indicative of increased vulnerability to developing CUD. However, there are other factors (as discussed below) that may explain why an increase in cannabis dependence was observed at the 10-year follow-up.

A later study using these data evaluated the probability and speed of going from first cannabis use to developing cannabis dependence as a function of the age of first use. The conditional probability of transition from cannabis use to dependence was estimated to be 6.2 percent (Behrendt et al., 2009). The authors also compared the time of transition from first substance use (nicotine, alcohol, or cannabis) to the development of the specific substance use disorder and found that the transition from first cannabis use to the development of CUD occurred at a faster rate than for those with alcohol or nicotine use disorders.

Other Variables Specific to Adolescents

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on variables that protect against or increase the risk of developing cannabis use disorders among adolescents.

Primary Literature Longitudinal data from the above-described community-based sample from Munich, Germany, were analyzed to determine whether the age of first alcohol and nicotine affects the risk of transition from cannabis use to cannabis dependence (Behrendt et al., 2012). This analysis took into account externalizing disorders (mental disorders characterized by disruptive behaviors that are directed toward an individual's external environment) and parental substance use disorders as potential factors that may affect the trajectory to cannabis dependence. Using multiple models, the authors found that (1) a younger age of cannabis use (hazard ratio [HR], 0.77), (2) paternal alcohol dependence (HR, 1.47), and (3) externalizing disorders (HR, 1.69) were all associated with a higher risk of developing cannabis dependence. Externalizing disorders were associated with a slower transition from initial cannabis use to cannabis dependence (HR main effect, 1.14; HR interaction effect, 1.17; 95% CI = 1.03–1.33; $p = 0.013$). A younger age of first alcohol use was also associated with a higher risk for developing cannabis dependence (HR, 0.88).

In participants who used nicotine first, younger age of cannabis use and maternal alcohol dependence were associated with a higher risk of developing cannabis dependence. As such, the age of first alcohol and nicotine use interacted with other risk factors, including the age of first cannabis use, externalizing disorders, and parental alcohol use, in contributing to the risks of developing CUD.

In a population-based longitudinal study of children between the ages of 6 and 12 with yearly assessments, CUD was assessed at ages 19 to 21 ($n = 1,803$) to define the overall prevalence rates of the disorder (Pingault et al., 2013). The authors further determined whether childhood inattention and hyperactivity symptoms of ADHD, including oppositional behaviors (e.g., hostile, disobedient, or defiant behaviors), and anxiety and depressive behaviors served as risk factors for developing CUD. Overall, cannabis abuse or dependence (high, moderate, or severe) affected 9.1 percent of the participants during young adulthood. Only oppositional behaviors contributed to the risk of developing CUD (OR, 2.33; 95% CI = 1.4–3.87), whereas anxiety and depressive disorders did not.

To determine early life-course predictors of problem cannabis use in early adulthood, data obtained from a population-based birth cohort study of 2,493 young adults who had been included in the Mater Hospital and University of Queensland Study of Pregnancy (MUSP) were assessed (Hayatbakhsh et al., 2009). In this population, 21 percent of those who ever used cannabis were classified as having a CUD at the 21-year follow-up assessment. Males were 2.5 times more likely to have a CUD than females; children living in a family with the mother reporting more frequent changes in marital status had an increased risk of CUD (OR, 2.9; 95% CI = 1.7–5.0); aggressive and delinquent children were 5.4 times more likely to develop CUD; those with poor school performance at 14 years of age were more likely to have CUD (OR, 3.4; 95% CI = 2.3–4.9); and maternal smoking when the child was 14 years of age also increased risk of CUD (OR, 2.0; 95% CI = 1.6–2.5). Childhood anxiety and depression were not risk factors for developing CUD.

In an effort to determine the association between cannabis use by 18 years of age and risk for CUD at 24 years of age, the frequency of cannabis use was evaluated in a 10-year representative cohort study set in Australia ($n = 1,520$ participants included in the final assessment), which included six surveys during adolescence (15–17.5 years of age) and two follow-up assessments during young adulthood (at 21 and 24 years of age) (Swift et al., 2008). One-third of the population reported having used cannabis during adolescence, and 37 percent of the adolescent cannabis users were using at least weekly when interviewed at 24 years of age. After adjusting for potential confounding factors, problem cannabis use at 24 years of age was associated with adolescent cannabis use, tobacco

use, and persistent mental health problems. The frequency of cannabis use was evaluated in a follow-up analysis that sought to determine whether moderation of cannabis use among adolescent cannabis users protected against the risk of CUD in young adulthood (Swift et al., 2009). In this study, participants were grouped into one of six categories that reflected their maximum level of adolescent use (i.e., nonusers, occasional to abstinence, occasional persisting, weekly to abstinence, weekly to occasional, and weekly persisting). The study's outcome measures were the level of cannabis use and DSM-IV cannabis dependence in youth adulthood. While 31 percent of the population reported having ever used cannabis, 71 percent of occasional users and 28 percent of weekly users were abstinent in young adulthood. Adolescent weekly or daily users who persisted with regular use (rather than decreased use or becoming abstinent) were at the greatest risk for developing CUD in young adulthood. Therefore, this suggests that moderating adolescent cannabis use can protect against the later problem use that is observed in persistent users. However, regardless of whether the adolescent users moderated their intake, the risk for developing CUD in young adulthood was still significantly greater for adolescent users than for those who never used cannabis.

The Christchurch Health and Development longitudinal birth cohort study ($n = 1,265$) from New Zealand assessed the probability of developing CUD by young adulthood as a function of various social and demographic factors (Boden et al., 2006). By 18 years of age, 4.7 percent of the population met criteria for cannabis dependence; that number increased to 12.5 percent by 25 years of age. The primary risk factors that predicted the development of CUD included being male and having poor academic performance. Respondents with four or more of the following risk factors had a 50 percent risk of developing cannabis dependence: (1) peer substance use, (2) parental history of a substance use disorder, (3) novelty seeking, (4) cigarette smoking, (5) childhood sexual abuse, and (6) conduct problems.

A longitudinal study of probands from the Oregon Adolescent Depression Project (final $n = 816$) assessed the prevalence and age of onset of CUD over four assessments between the ages of 16 and 30 (Farmer et al., 2015). The weighted lifetime prevalence of CUD before the age of 30 was estimated to be 19.1 percent; 81.8 of these participants achieved recovery from CUD, and the recurrence rate of CUD was 27.7 percent, which likely occurred within 36 months following the offset of the first CUD diagnosis. Males were more likely to have been diagnosed at some point during their lives than females.

The association between psychopathology and problem cannabis use was also assessed in a longitudinal prospective study of adolescents ($n = 1,395$) that were 14 to 17 years of age at baseline and who were assessed

at three different time points over the course of 10 years (Wittchen et al., 2007). A prospective analysis determined that mood disorders (OR, 2.5; 95% CI = 1.3–4.7), including bipolar disorder (hypomania and mania) (OR, 2.7; 95% CI = 1.1–6.2), but not including dysthymia (chronic depression) (OR, 2.3; 95% CI = 0.7–6.7), predicted progression to CUD. Generalized anxiety disorder and specific phobias were also associated with CUD (OR, 3.9; 95% CI = 1.1–13.8 and OR, 1.8; 95% CI = 1.1–3.0, respectively). Of note, ADHD, posttraumatic stress disorder (PTSD), and panic/anxiety all failed to predict the development of CUD.

Data from a longitudinal survey of a representative sample ($n = 2,032$) of secondary students in the Australian state of Victoria who were assessed for cannabis disorders six times between the ages of 14 and 17 from 1992–1995 and again at 20 years of age were evaluated to determine the adolescent precursors of young adult cannabis dependence (Coffey et al., 2003). Variables that independently predicted cannabis dependence in young adulthood included being male (OR = 2.6; $p < 0.01$), regular cannabis use during adolescence (weekly use: OR = 4.9; daily use: OR = 4.6; $p = 0.02$), persistent antisocial behavior (linear effect $p = 0.03$), and persistent cigarette smoking (linear effect $p = 0.02$). Psychiatric comorbidity did not predict cannabis dependence (linear effect, $p = 0.26$). Regular cannabis use during adolescence only increased the risk for CUD in the absence of persistent problem alcohol use.

Discussion of Findings

Overall findings suggest that both biological sex and the age of initiation of cannabis use are positively associated with the development of problem cannabis use. There is also evidence that being male and smoking cigarettes are risk factors that contribute to the progression to problem cannabis use. Additional risk factors for the development of CUD during adolescence that are supported by moderate evidence include frequency of use, oppositional behaviors, younger age of first alcohol use, nicotine use, parental substance use, poor school performance, and childhood sexual abuse. The strength of association between the risk factors for developing problem cannabis use, including other drug use and psychopathology, differs between adult and adolescent onset of cannabis use. It is important to highlight that the studies reviewed above vary in their age grouping and generally include populations that cross from late adolescence into young adulthood. Therefore, the conclusions below pertain to a mixture of age subgroups, including older adolescents and young adults.

One significant limitation of any conclusions drawn from the current literature is that the data on cannabis use, other drug use, and the symptoms of problem cannabis use are derived from self-reports. Another

concern is that the structured interviews used to assess baseline dependent variables (i.e., mental health) and outcomes (i.e., problem cannabis use) vary between studies, and even for some longer longitudinal studies, within individual studies. Also, as mentioned in the first section, understanding the conclusions drawn from the currently available literature should take into account the fact that trends in cannabis use have evolved over the last 10 years and that the strength of cannabis has increased, which likely affects the strength of associations between risk factors and developing problem cannabis use. It is also important to note that there is biological plausibility for many of the risk factors noted above. Specifically, there is preclinical literature that speaks to the sex-dependent effects, exposure to nicotine as a risk factor for CUD, and the age of initiation of use affecting CUD.

CONCLUSION 13-2

Anxiety and Depression

- 13-2(a) There is limited evidence that childhood anxiety and childhood depression are risk factors for the development of problem cannabis use.**
- 13-2(b) There is moderate evidence that anxiety, personality disorders, and bipolar disorders are not risk factors for the development of problem cannabis use.**
- 13-2(c) There is moderate evidence that major depressive disorder is a risk factor for the development of problem cannabis use.**

ADHD

- 13-2(d) There is moderate evidence that adolescent attention deficit hyperactivity disorder (ADHD) is not a risk factor for the development of problem cannabis use.**
- 13-2(e) There is substantial evidence that stimulant treatment of ADHD during adolescence is not a risk factor for the development of problem cannabis use.**

Biological Sex

13-2(f) There is moderate evidence that being male is a risk factor for the development of problem cannabis use.

Other Drug Use

13-2(g) There is moderate evidence that exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use.

13-2(h) There is moderate evidence that neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use.

13-2(i) There is substantial evidence that being male and smoking cigarettes are risk factors for the progression of cannabis use to problem cannabis use.

Age

13-2(j) There is substantial evidence that initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use.

13-2(k) There is moderate evidence that during adolescence the frequency of cannabis use, oppositional behaviors, a younger age of first alcohol use, nicotine use, parental substance use, poor school performance, antisocial behaviors, and childhood sexual abuse are risk factors for the development of problem cannabis use.

**Are There Risk and Protective Factors for Severity
or Persistence of Problem Cannabis Use?**

Psychopathology

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on psychopathology as a risk or a protective factor for the severity or persistence of problem cannabis use.

Primary Literature A case-control study sought to determine the association between a history of psychiatric treatment and persistent cannabis

use disorder (Arendt et al., 2007). Data from the Danish Psychiatric Case Register ($n = 3,114$; mean age at start of treatment = 25.7 years) were compared to a representative control group that was randomly selected from the general population and matched to the patient population for age and biological sex ($n = 15,570$). The authors determined that a history of psychiatric treatment was associated with increased rates of reentry into substance abuse treatment for cannabis dependence (OR, 1.26; 95% CI = 1.07–1.48) relative to the control population.

In an Israeli population ($n = 1,317$; ages ranged from 21–45 years and older), Walsh et al. (2014) conducted in-person structured interviews to examine the association between traumatic exposure and substance dependence (alcohol, nicotine, and marijuana) and to assess whether PTSD accounted for this association. After controlling for alcohol and nicotine dependence, investigators found that PTSD symptoms were associated with increased odds of marijuana dependence (OR, 1.1; 95% CI = 1.04–1.24) and concluded that the severity of PTSD symptoms may increase the risk for substance dependence. It should be noted, however, that these are cross-sectional data and that the directionality and causality of these associations cannot be determined.

A study by Boden et al. (2013) was outside the scope of our primary literature search due to its small sample size, but it was included because of its potential relevance to the committee's prioritized research question. In this study, researchers found that in a small population of cannabis-dependent military veterans ($n = 37$; mean age of starting sample = 51.3 years), a diagnosis of PTSD was significantly associated with the use of cannabis to cope with PTSD symptoms, the severity of cannabis withdrawal, and three factors of cannabis drug craving (i.e., compulsivity, emotionality, and anticipation) relative to a cannabis-dependent population without a diagnosis of PTSD ($n = 57$). Furthermore, the severity of PTSD symptoms was associated with an increased severity of cannabis withdrawal and factors of cannabis craving (i.e., compulsivity, emotionality, and anticipation).

Biological Sex

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on biological sex as a risk or a protective factor for the severity or persistence of problem cannabis use.

Primary Literature Data from the NLAES ($n = 42,862$) were analyzed in an effort to determine the effect of biological sex on the risk and severity of cannabis use disorders (Grant et al., 2006). Of the participants who reported cannabis use at least 12 times, women were less likely to be cat-

egorized with cannabis “abuse/moderate dependence” than men (8 percent versus 14 percent) or “severe abuse/dependence” (3 percent versus 6 percent). While men were consistently more likely than women to report hazardous cannabis use, women were more likely to report withdrawal and to have higher rates of four symptoms of dependence in the “abuse/moderate dependence” category.

A longitudinal study of probands from the Oregon Adolescent Depression Project (final $n = 816$) assessed recovery from CUD as a function of biological sex (Farmer et al., 2015). Females achieved recovery from CUD at a significantly faster rate than males (females = 24.2 months, standard deviation [SD] = 24.8; males = 41.2 months, SD = 42.7; $p = .006$), although recurrence rates of CUD did not differ between males and females (30.0% of males, 25.4% of females, $p = 0.564$).

Discussion of Findings

In addition to the limitations cited for the first two sections such as issues with self-reported cannabis use, the respondents’ reporting of symptoms of problem cannabis use, and data restricted to trends of cannabis use and cannabis strength that do not accurately reflect current trends, the current findings are additionally restricted to limited follow-up with participants and to only a few of the risk factors highlighted in the second section, including biological sex. The impact of the primary risk factors for developing problem cannabis use identified in the second section of this chapter, including the age of initiation of use, biological sex, and other drug use, should be explored as risk factors for both the severity and the recurrence of problem cannabis use over extended periods of time.

CONCLUSION 13-3

13-3(a) There is moderate evidence of a statistical association between the persistence of problem cannabis use and a history of psychiatric treatment.

13-3(b) There is substantial evidence of a statistical association between being male and the severity of problem cannabis use, but the recurrence of problem cannabis use does not differ between males and females.

13-3(c) There is moderate evidence of a statistical association between problem cannabis use and increased severity of posttraumatic stress disorder symptoms.

RESEARCH GAP

To address the research gaps relevant to problem cannabis use, the committee suggests the following:

- The impact of the primary risk factors for developing problem cannabis use needs to be explored as risk factors for both the severity and the recurrence of problem cannabis use over extended periods of time.

SUMMARY

This chapter outlines the committee's efforts to review the current evidence base (1) to determine likelihood of developing problem cannabis use and (2) to identify the potential risk and protective factors involved in the development or exacerbation of problem use. The vast majority of the conclusions formed within this chapter were of moderate evidence; however, the conclusions that were determined to have substantial evidence were formed by research that examined the impact of biological sex, cannabis use at an early age, and past use of cannabis on problem cannabis use. Many of the chapter conclusions pertain to a mixture of age groups, including older adolescents and young adults. See Box 13-1 for a summary list of the chapter's conclusions.

These research conclusions may have important public health implications; however, it is important that the conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections above. It is also important to understand that the conclusions drawn from the currently available literature should take into account the fact that trends of cannabis use have evolved over the past 10 years and note that the strength of cannabis has increased, which likely has affected strength of associations between risk factors and developing problem cannabis use. Greater attention to the research limitations (e.g., reliance on self-reported cannabis use, limited detail on the amount of cannabis used per occasion, polydrug use, limited follow-up, and so on) and improvements to study design and methodological approach would bolster the evidence base and help ensure that substantial evidence concerning problem cannabis use is available.

BOX 13-1 Summary of Chapter Conclusions*

There is substantial evidence that:

- Stimulant treatment of attention deficit hyperactivity disorder (ADHD) during adolescence is *not* a risk factor for the development of problem cannabis use (13-2e)
- Being male and smoking cigarettes are risk factors for the progression of cannabis use to problem cannabis use (13-2i)
- Initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use (13-2j)

There is substantial evidence of a statistical association between:

- Increases in cannabis use frequency and the progression to developing problem cannabis use (13-1)
- Being male and the severity of problem cannabis use, but the recurrence of problem cannabis use does not differ between males and females (13-3b)

There is moderate evidence that:

- Anxiety, personality disorders, and bipolar disorders are *not* risk factors for the development of problem cannabis use (13-2b)
- Major depressive disorder is a risk factor for the development of problem cannabis use (13-2c)

REFERENCES

- APA (American Psychiatric Association). 2013. *Diagnostic and statistical manual of mental disorders, 5th ed.* Arlington, VA: American Psychological Association.
- Arendt, M., R. Rosenberg, L. Foldager, G. Perto, and P. Munk-Jorgensen. 2007. Psychopathology among cannabis-dependent treatment seekers and association with later substance abuse treatment. *Journal of Substance Abuse Treatment* 32(2):113–119.
- Behrendt, S., H. U. Wittchen, M. Hofler, R. Lieb, and K. Beesdo. 2009. Transitions from first substance use to substance use disorders in adolescence: Is early onset associated with a rapid escalation? *Drug and Alcohol Dependence* 99(1-3):68–78.
- Behrendt, S., K. Beesdo-Baum, M. Hofler, A. Perkonig, G. Buhringer, R. Lieb, and H. U. Wittchen. 2012. The relevance of age at first alcohol and nicotine use for initiation of cannabis use and progression to cannabis use disorders. *Drug and Alcohol Dependence* 123(1-3):48–56.
- Blanco, C., D. S. Hasin, M. M. Wall, L. Florez-Salamanca, N. Hoertel, S. Wang, B. T. Kerridge, and M. Olfson. 2016. Cannabis use and risk of psychiatric disorders: Prospective evidence from a U.S. national longitudinal study. *JAMA Psychiatry* 73(4):388–395.

- Adolescent ADHD is *not* a risk factor for the development of problem cannabis use (13-2d)
- Being male is a risk factor for the development of problem cannabis use (13-2f)
- Exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use (13-2g)
- Neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use (13-2h)
- During adolescence the frequency of cannabis use, oppositional behaviors, a younger age of first alcohol use, nicotine use, parental substance use, poor school performance, antisocial behaviors, and childhood sexual abuse are risk factors for the development of problem cannabis use (13-2k)

There is moderate evidence of a statistical association between:

- A persistence of problem cannabis use and a history of psychiatric treatment (13-3a)
- Problem cannabis use and increased severity of posttraumatic stress disorder symptoms (13-3c)

There is limited evidence that:

- Childhood anxiety and childhood depression are risk factors for the development of problem cannabis use (13-2a)

* Numbers in parentheses correspond to chapter conclusion numbers.

Blazer, D. G., and L. T. Wu. 2009. The epidemiology of substance use and disorders among middle aged and elderly community adults: National Survey on Drug Use and Health. *American Journal of Geriatric Psychiatry* 17(3):237–245.

Boden, J. M., D. M. Fergusson, and L. J. Horwood. 2006. Illicit drug use and dependence in a New Zealand birth cohort. *Australian and New Zealand Journal of Psychiatry* 40(2):156–163.

Boden, M. T., K. A. Babson, A. A. Vujanovic, N. A. Short, and M. O. Bonn-Miller. 2013. Posttraumatic stress disorder and cannabis use characteristics among military veterans with cannabis dependence. *American Journal on Addictions* 22(3):277–284.

Bovasso, G. B. 2001. Cannabis abuse as a risk factor for depressive symptoms. *American Journal of Psychiatry* 158(12):2033–2037.

Casajuana, C., H. López-Pelayo, M. M. Balcels, L. Miguel, J. Colom, and A. Gual. 2016. Definitions of risky and problematic cannabis use: A systematic review. *Substance Use & Misuse* 51(13):1760–1770.

CBHSQ (Center for Behavioral Health Statistics and Quality). 2015. *Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health* (HHS Publication No. SMA 15-4927, NSDUH Series H-50). <http://www.samhsa.gov/data> (accessed November 21, 2016).

- Chen, C. Y., M. S. O'Brien, and J. C. Anthony. 2005. Who becomes cannabis dependent soon after onset of use? Epidemiological evidence from the United States: 2000–2001. *Drug and Alcohol Dependence* 79(1):11–22.
- Coffey, C., J. B. Carlin, M. Lynskey, N. Li, and G. C. Patton. 2003. Adolescent precursors of cannabis dependence: Findings from the Victorian Adolescent Health Cohort Study. *British Journal of Psychiatry* 182:330–336.
- Compton, W. M., B. F. Grant, J. D. Colliver, M. D. Glantz, and F. S. Stinson. 2004. Prevalence of marijuana use disorders in the United States: 1991–1992 and 2001–2002. *JAMA* 291(17):2114–2121.
- Cogle, J. R., J. K. Hakes, R. J. Macatee, M. J. Zvolensky, and J. Chavarria. 2016. Probability and correlates of dependence among regular users of alcohol, nicotine, cannabis, and cocaine: Concurrent and prospective analyses of the National Epidemiologic Survey on Alcohol and Related Conditions. *Journal of Clinical Psychiatry* 77(4):e444–e450.
- Daniulaityte, R., R. W. Nahhas, S. Wijeratne, R. G. Carlson, F. R. Lamy, S. S. Martins, E. W. Boyer, G. A. Smith, and A. Sheth. 2015. Time for dabs: Analyzing Twitter data on marijuana concentrates across the U.S. *Drug and Alcohol Dependence* 155:307–311.
- ElSohly, M. A., Z. Mehmedic, S. Foster, C. Gon, S. Chandra, and J. C. Church. 2016. Changes in cannabis potency over the last 2 decades (1995–2014): Analysis of current data in the United States. *Biological Psychiatry* 79(7):613–619.
- Farmer, R. F., D. B. Kosty, J. R. Seeley, S. C. Duncan, M. T. Lynskey, P. Rohde, D. N. Klein, and P. M. Lewinsohn. 2015. Natural course of cannabis use disorders. *Psychological Medicine* 45(1):63–72.
- Feingold, D., M. Weiser, J. Rehm, and S. Lev-Ran. 2016. The association between cannabis use and anxiety disorders: Results from a population-based representative sample. *European Neuropsychopharmacology* 26(3):493–505.
- Grant, J. D., J. F. Scherrer, R. J. Neuman, A. A. Todorov, R. K. Price, and K. K. Bucholz. 2006. A comparison of the latent class structure of cannabis problems among adult men and women who have used cannabis repeatedly. *Addiction* 101(8):1133–1142.
- Haberstick, B. C., S. E. Young, J. S. Zeiger, J. M. Lessem, J. K. Hewitt, and C. J. Hopfer. 2014. Prevalence and correlates of alcohol and cannabis use disorders in the United States: Results from the National Longitudinal Study of Adolescent Health. *Drug and Alcohol Dependence* 136:158–161.
- Hartz, S. M., C. N. Pato, H. Medeiros, P. Cavazos-Rehg, J. L. Sobell, J. A. Knowles, L. J. Bierut, and M. T. Pato. 2014. Comorbidity of severe psychotic disorders with measures of substance use. *JAMA Psychiatry* 71(3):248–254.
- Hasin, D. S., T. D. Saha, B. T. Kerridge, R. B. Goldstein, S. P. Chou, H. Zhang, J. Jung, R. P. Pickering, W. J. Ruan, S. M. Smith, B. Huang, and B. F. Grant. 2015. Prevalence of marijuana use disorders in the United States between 2001–2002 and 2012–2013. *JAMA Psychiatry* 72(12):1235–1242.
- Hayatbakhsh, M. R., J. M. Najman, W. Bor, M. J. O'Callaghan, and G. M. Williams. 2009. Multiple risk factor model predicting cannabis use and use disorders: A longitudinal study. *American Journal of Drug and Alcohol Abuse* 35(6):399–407.
- Humphreys, K. L., T. Eng, and S. S. Lee. 2013. Stimulant medication and substance use outcomes: A meta-analysis. *JAMA Psychiatry* 70(7):740–749.
- Kedzior, K. K., and L. T. Laeber. 2014. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population—A meta-analysis of 31 studies. *BMC Psychiatry* 14:136.
- Kilmer, B., J. P. Caulkins, G. Midgette, L. Dahlkemper, R. J. MacCoun, and R. L. Pacula. 2013. *Before the grand opening: Measuring Washington State's marijuana market in the last year before legalized commercial sales*. Santa Monica, CA: RAND Corporation.

- Pacek, L. R., S. S. Martins, and R. M. Crum. 2013. The bidirectional relationships between alcohol, cannabis, co-occurring alcohol and cannabis use disorders with major depressive disorder: Results from a national sample. *Journal of Affective Disorders* 148(2-3):188–195.
- Pacula, R. L., M. Jacobson, and E. J. Maksabedian. 2016. In the weeds: A baseline view of cannabis use among legalizing states and their neighbours. *Addiction* 111(6):973–980.
- Perkonig, A., R. D. Goodwin, A. Fiedler, S. Behrendt, K. Beesdo, R. Lieb, and H. U. Wittchen. 2008. The natural course of cannabis use, abuse and dependence during the first decades of life. *Addiction* 103(3):439–449.
- Pingault, J. B., S. M. Cote, C. Galera, C. Genolini, B. Falissard, F. Vitaro, and R. E. Tremblay. 2013. Childhood trajectories of inattention, hyperactivity and oppositional behaviors and prediction of substance abuse/dependence: A 15-year longitudinal population-based study. *Molecular Psychiatry* 18(7):806–812.
- Silins, E., L. J. Horwood, G. C. Patton, D. M. Fergusson, C. A. Olsson, D. M. Hutchinson, E. Spry, J. W. Toumbourou, L. Degenhardt, W. Swift, C. Coffey, R. J. Tait, P. Letcher, J. Copeland, R. P. Mattick, S. Allsop, W. Hall, R. Hayatbakhsh, K. Little, J. Najman, R. Skinner, and T. Slade. 2014. Young adult sequelae of adolescent cannabis use: An integrative analysis. *The Lancet Psychiatry* 1(4):286–293.
- Swift, W., C. Coffey, J. B. Carlin, L. Degenhardt, and G. C. Patton. 2008. Adolescent cannabis users at 24 years: Trajectories to regular weekly use and dependence in young adulthood. *Addiction* 103(8):1361–1370.
- Swift, W., C. Coffey, J. B. Carlin, L. Degenhardt, B. Calabria, and G. C. Patton. 2009. Are adolescents who moderate their cannabis use at lower risk of later regular and dependent cannabis use? *Addiction* 104(5):806–814.
- Walsh, K., J. C. Elliott, D. Shmulewitz, E. Aharonovich, R. Strous, A. Frisch, A. Weizman, B. Spivak, B. F. Grant, and D. Hasin. 2014. Trauma exposure, posttraumatic stress disorder and risk for alcohol, nicotine, and marijuana dependence in Israel. *Comprehensive Psychiatry* 55(3):621–630.
- WHO (World Health Organization). 2015. *The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines*. Geneva, Switzerland: World Health Organization.
- Wittchen, H. U., C. Frohlich, S. Behrendt, A. Gunther, J. Rehm, P. Zimmermann, R. Lieb, and A. Perkonig. 2007. Cannabis use and cannabis use disorders and their relationship to mental disorders: A 10-year prospective-longitudinal community study in adolescents. *Drug and Alcohol Dependence* 88(Suppl. 1):S60–S70.

14

Cannabis Use and the Abuse of Other Substances

Chapter Highlight

- Cannabis use is likely to increase the risk for developing substance dependence (other than cannabis use disorder).

Since the 1970s, researchers have debated about the role that cannabis may play in the “gateway hypothesis,” which suggests that individuals rarely use certain substances, such as heroin or cocaine, without first having used “gateway” substances, such as alcohol, tobacco, or cannabis (Kandel, 1975; Vanyukov et al., 2012). While some research has shown an association between cannabis use and the subsequent use of other illicit drugs, the predictors of progression from cannabis use to other illicit drugs remain largely unknown (Secades-Villa et al., 2015). Emerging animal studies have begun to explore the hypothesis that cannabis exposure may enhance the susceptibility to the addictive effects of other drugs (Panlilio et al., 2012). Researchers have also begun to explore the “reverse gateway hypothesis.” This hypothesis posits that cannabis use is a reverse gateway to the initiation of other addictive drugs such as nicotine and alcohol (Agrawal et al., 2008).

In the United States, the number of individuals 12 years and older using illicit drugs rose each year between 2002 and 2013. In 2014 alone, the National Survey on Drug Use and Health reported that in this age range 27 million individuals—or almost 1 in every 10 Americans—were found

to have used illicit drugs within the past 30 days, 66.9 million were current users of tobacco, and another 139.7 million were past-month alcohol drinkers (CBHSQ, 2015). With illicit drug use on the rise, the need for understanding and addressing when and how individuals start using illicit drugs is of the utmost importance. Of similar importance is understanding the role that cannabis might play in the use of other addictive substances such as tobacco and alcohol.

The committee responsible for the 1999 Institute of Medicine (IOM)¹ report *Marijuana and Medicine: Assessing the Science Base* discussed the “gateway hypotheses” but did not make any specific conclusions about its relevance to cannabis use. That report questioned the designation of cannabis as a “gateway” drug because its use is often preceded by underage drinking and tobacco use, and no conclusive evidence supporting a causal link between cannabis use and the use of other illicit drugs was found at that time (IOM, 1999).

In this chapter, the committee reviews the research evidence that most directly addresses the prioritized research questions related to the associations among cannabis use and (1) the initiation of use of other substances, (2) changes in the rates and use patterns of other substances and, (3) and the development of other substance dependence or substance abuse disorder. Due to the time constraints of the study, additional search constraints were added to prioritize the types of studies that would likely produce the clearest research conclusions. For example, literature searches were limited to articles that included the search terms “longitudinal,” “prospective,” and “case-control,” and the committee did not review controlled laboratory studies with cannabis. Although the committee did not find any fair- or good-quality systematic reviews covering these issues, 12 primary articles published since the 1999 IOM report were identified and are reviewed in this chapter.

ABUSE OF OTHER SUBSTANCES

Is There an Association Between Cannabis Use and the Initiation of Use of Other Substances?

Tobacco/Nicotine

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the initiation of tobacco/nicotine use.

¹ As of March 2016, the Health and Medicine Division continues the consensus studies and convening activities previously carried out by the Institute of Medicine (IOM).

Primary Literature Mayet and colleagues (2016) conducted a retrospective cohort study of the transitions between tobacco, cannabis, and other illicit drugs initiations. Data on 16,421 adults ages 18 to 34 were collected from two French nationwide health and behavior studies conducted in 2005 and 2010. The data used included the age of initiation of substance use (cannabis, tobacco, alcohol, other illicit drugs), current use, and a number of other variables (e.g., gender, socioeconomic level). A total of 436,206 observations based on yearly measures were provided by the study subjects, including 17,510 transitions from one state of use to another. A Markov multistate model was constructed to examine transitions from cannabis use to the use of other drugs. The model's results show that the probability of initiating tobacco after cannabis use (10.39 percent) was significantly greater ($p < 0.001$) than the probability of initiating cannabis after tobacco use (3.47 percent). The primary study limitations include potential recall bias on the age of initiation and the usual issues surrounding the self-reporting of substance use.

Mayet and colleagues (2011) analyzed data collected from a cross-sectional survey of 29,393 17-year-old adolescents attending a compulsory military information session to assess transitions from cannabis use to the use of other substances. Data from study participants were captured via a self-administered questionnaire on substance use; thus, participants were considered followed from birth through 2011 by way of recall data. Substance use was categorized as "no lifetime use of tobacco and cannabis," "tobacco initiation only," "cannabis initiation only," "daily use of tobacco only," "daily use of cannabis only," or "daily use of both tobacco and cannabis" (Mayet et al., 2011, p. 1102). A Markov multistate model was constructed to examine the transition states among the first-substance-use cohorts from no use/initial substance use to other substance use states.

Study participants were more likely to use tobacco (72.2 percent) than cannabis (49.4 percent), and only 2 percent of those using both tobacco and cannabis reported having used cannabis before tobacco (Mayet et al., 2011). With respect to transitions from initial substance use, the risk of initiating tobacco use from no lifetime use was 17.6 times greater (95% confidence interval [CI] = 16.5–18.9) than first initiating cannabis use. Among individuals initiating use with cannabis, the transition to first tobacco use was 3.2 times greater (95% CI = 2.9–3.6) than the transition from no lifetime use of cannabis to first tobacco use (Mayet et al., 2011). However, the transition of first tobacco use to cannabis was 42.1 times greater (95% CI = 39.3–45.1) than the transition from no lifetime use of tobacco to first cannabis use. The transition from daily use of cannabis to daily use of both cannabis and tobacco was 3.0 times greater (95% CI = 2.0–4.4) than the transition from daily tobacco use to daily use of both cannabis and tobacco (Mayet et al., 2011). The authors also found that

cannabis initiation did not increase the risk of a tobacco user transitioning to a daily cannabis smoker. The study's limitations include potential problems with recall bias and self-reporting of substance use.

Opioids

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the initiation of use of opioids.

Primary Literature In the retrospective cohort study described earlier, Mayet and colleagues (2016) also explored the transition from cannabis use to the use of other illicit drugs. They found that the probability of initiating other illicit drugs after cannabis did not differ significantly from the probability of starting with other illicit drugs.

Mixed Drug Use

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the initiation of use of other substances.

Primary Literature Novins and Barón (2004) reported on risk factors for the initiation of substance use and transition to other substance use among American Indian adolescents living west of the Mississippi. Survey data collected as part of the Voices of Indian Teens longitudinal study from 1993 to 1996 were used to calculate the conditional probability that an adolescent who reported lifetime use of cannabis (Stage 1) would progress to report a lifetime use of stimulants, sedatives, cocaine, or other drugs such as hallucinogens, phencyclidine, or heroin (Stage 2).

For analysis purposes, the initial sample of 2,356 adolescents was reduced to 1,244 adolescents due to exclusions related to continued lifetime abstinence or transition to Stage 2 before the study began and to inconsistent responses between the two waves of data collection, as well as those lost to follow-up (Novins and Barón, 2004). The hazard ratio (HR) for the progression of cannabis use (Stage 1) to a harder substance (Stage 2) was 2.737 ($p < 0.01$). The authors noted that the study had a number of limitations, including generalizability to other populations, the self-reporting of substance use data, an inability to include tobacco use in the analysis because the survey did not differentiate between ceremonial and non-ceremonial tobacco use, and the potential for underestimating the results because of the potential bias created by individuals lost to

follow-up who may have had different (higher) patterns of substance use than those remaining in the study.

Discussion of Findings

The small number of studies reviewed provide limited evidence that cannabis use increases the rates of initiation of other drug use, mainly tobacco. Two studies had relatively large samples. The data do not provide compelling evidence that cannabis is associated with the initiation of other drugs of abuse, although this is one possibility. Other possibilities that could explain these findings include easier access to cannabis than to other illicit substances and common risk factors for both cannabis use and the use of other substances. Although cannabis use is associated with increased odds of transitioning to tobacco use relative to non-cannabis users, tobacco use was associated with far greater odds of transitioning to cannabis use relative to non-tobacco users. These data highlight tobacco use as a key risk factor for the initiation of cannabis use.

CONCLUSION 14-1 There is limited evidence of a statistical association between cannabis use and the initiation of tobacco use.

Is There an Association Between Cannabis Use and the Rates and Use Patterns of Other Substances?

Alcohol

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the rates and use patterns of drinking alcohol.

Primary Literature Buu and colleagues (2015) conducted a secondary data analysis of eight waves of data collected from 850 high-risk adolescents participating in the longitudinal Flint Adolescent Study to assess risk and protective factors for substance use and other health risk behaviors through adulthood (i.e., ages 14–24 years). The impact of early or later onset (i.e., age at first use) and of the quantity and frequency of cannabis use on heavy drinking were specific research questions. A linear mixed model was used to determine the longitudinal effects of nicotine and marijuana on heavy drinking while controlling for the early onset of alcohol use. Model results indicate that both early onset cannabis users (β , 0.2263; standard error [SE] = 0.0445; $p < 0.0001$), late onset cannabis users (β , 0.1838; SE = 0.0461; $p < 0.0001$), and those who used cannabis more

frequently (β , 0.2667; SE = 0.0119; $p < 0.0001$) were all at a higher risk of heavy alcohol drinking than those who did not use cannabis at all (Buu et al., 2015). Among this population, about 80 percent of the study participants were black and had grade point averages of 3.0 or below and thus are not representative of the general youth population. Furthermore, the lifetime prevalence of substance use was higher in the study population than in the general population. The impact of cannabis use on nicotine use was not reported.

Opioids

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the rates and use patterns of opioids.

Primary Literature In a longitudinal study of a random sample of 120 adolescents ages 12 to 18 years who were admitted to a level 1 trauma center or an emergency department for injury, Whiteside and colleagues (2016) found that preinjury cannabis use was an independent predictor of continued prescription opioid use up to 12 months after discharge (relative risk, 1.69; 95% CI = 1.09–2.6). Cannabis use was assessed via a single-item question regarding cannabis use (yes/no) in the year before the injury, and the use of a range of prescription opioids (codeine, hydrocodone, oxycodone, etc.) was assessed and categorized as yes or no at months 2, 5, and 12. At 1 year post injury, 12.5 percent of adolescents were still using prescribed opioids. The study's limitations include the use of self-reported data to determine preinjury cannabis use and opioid use, the reliance on a small study sample, and the fact that the sample was collected at an urban academic trauma center, which thus limited the generalizability of the findings.

Tobacco/Nicotine

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the rates and use patterns of tobacco and nicotine dependence.

Primary Literature Agrawal and colleagues (2008) studied women cannabis users and patterns of smoking and nicotine dependence. Data were collected as part of the Missouri Adolescent Female Twin Study (MOAFTS), a cohort study of 3,787 young adult twin females ages 18 to 29 years, who were originally interviewed in 1994–1999 and subsequently reinterviewed in 2002–2005. Data collection included lifetime cannabis

use (ever used cannabis and other measures of frequency and use) and cannabis dependence (determined by a lifetime history of one or more of four *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [DSM-IV] abuse criteria or one or more of six DSM-IV dependence criteria). Regular cigarette smoking among participants was determined by responding positively to having smoked 100 or more cigarettes lifetime and smoking 20–99 cigarettes at least once per week for a period of 2 months or longer. Nicotine dependence was defined using the seven DSM-IV dependence criteria, with at least three symptoms clustering within the same 12-month period. Data on a number of covariates were also collected, including measures of behavioral disinhibition, negative affect regulation, and other measures of psychopathology. In this sample, 44.2 percent of the participants were cannabis users, 34.7 percent were classified as regular cigarette smokers, and 17.4 percent were designated as nicotine dependent based on DSM-IV criteria. It is also important to note that only 6.8 percent of participants reported smoking their first cigarette before using cannabis for the first time.

Survival analyses were used to examine whether women who smoked cannabis were at an increased risk of moving from experimenting with smoking (but not first time smoking) to becoming a regular smoker. After adjusting for covariates, the results indicate that women with a prior history of cannabis use were 4.4 times more likely (HR, 4.41; 95% CI = 3.57–5.44) to transition from experimenting with smoking to becoming regular smokers. An additional analysis was conducted to assess spurious associations caused by the onset of cannabis use and regular smoking in the same year. The results of this analysis showed a diminished effect size; the effect size of the hazards of regular smoking in cannabis users was reduced to 1.8 (95% CI = 1.5–2.2) for those meeting this condition.

Mixed Drug Use

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the rates and use patterns of substances other than cannabis.

Primary Literature To examine trajectories of adolescent cannabis and alcohol users Patton and colleagues (2007) analyzed data from a 10-year cohort study of health in 2,032 adolescents and young adults living in Victoria, Australia. Data were collected in eight waves over the study period from an initial study sample of adolescents who were in mid-secondary school in 1992. About 95 percent of students from the initial study sample participated in Waves 1 through 6, and 75 percent of the students participated in Wave 8. The frequency of cannabis and alcohol

use was categorized in three categories: “any alcohol or cannabis use,” “at least moderate-risk alcohol or cannabis use,” and “high-risk alcohol or cannabis use” (Patton et al., 2007, p. 609). Logistic regression modeling was used to explore the associations between substance use in adolescence (at about 15 years old in Wave 1) and later substance use in early adulthood (at about 25 years old in Wave 8).

After adjusting for a number of social and behavioral factors and persistent substance use measures, the researchers found that adolescents with moderate-risk cannabis use were seven times as likely to develop high-risk cannabis use (odds ratio [OR], 7.4; 95% CI = 3.3–17) and twice as likely to develop high-risk alcohol use in early adulthood (OR, 2.2; 95% CI = 1.1–4.5) compared with students with no hazardous alcohol use or daily cannabis use (Patton et al., 2007).

Among this population, the risk was also elevated for daily cigarette smoking (OR, 3.0; 95% CI = 1.7–5.4), for the use of amphetamines (OR, 6.0; 95% CI = 3.6–10.0), for the use of ecstasy (OR, 7.2; 95% CI = 4.3–12.0), and for the use of cocaine (OR, 4.7; 95% CI = 2.3–9.7) within the past 12 months, as reported in Wave 8 (Patton et al., 2007). The study’s limitations include a 25 percent reduction in the initial sample between Wave 1 and Wave 8 (imputation techniques were used to mitigate potential bias related to students missing waves of the survey), the use of self-reports to determine substance use, and questions about the generalizability of the study to other populations.

The use of cannabis and relapse after discharge from a substance abuse program were the focus of a study conducted by Aharonovich and colleagues (2005). This longitudinal study followed 349 patients who had undergone and successfully completed inpatient treatment for a DSM-IV diagnosis of alcohol, cocaine, or heroin dependence; patients had not experienced mania or non-affective psychosis. Patients were followed up after discharge at months 6, 12, and 18 to update the Psychiatric Research Interview for Substance and Mental Disorders. Responses were analyzed to assess cannabis use and return to substance abuse, sustained remission from substance abuse, and relapse to substance abuse after sustained remission. Of the 349 patients participating in the study, 250 contributed data through at least one follow-up interview; the study results are based on this subset of patients. Of the 250 patients dependent on alcohol, cocaine, or heroin at baseline who did not achieve sustained remission from using these substances, 41.4 percent used cannabis during follow-up after hospital discharge compared to 15.4 percent of those who had achieved remission ($p < 0.0001$) (Aharonovich et al., 2005). Among the patients dependent on alcohol at baseline who failed to achieve sustained remission, 38.7 percent used cannabis ($p < 0.004$), and among patients dependent on cocaine at baseline who failed to achieve sustained remis-

sion, 52.5 percent used cannabis during follow-up after hospital discharge ($p < 0.03$). Relapse after sustained remission was also seen among patients who used cannabis during follow-up.

A Cox proportional model that adjusted for sociodemographic variables and diagnoses of substance dependence and a number of psychiatric symptoms and disorders was developed to examine the effects of cannabis use on a number of outcomes, including the return to substance use (multiple substance use, alcohol only, cocaine only, and heroin only), sustained remission from substance use, and relapse to substance use. HRs were significant ($p < 0.0001$) for cannabis use and a return to the use of multiple substances, alcohol only, and cocaine only. Cannabis use was associated with a statistically significant reduced hazard of achieving a sustained remission from multiple substance use and cocaine use specifically ($p < 0.05$). In addition, cannabis use was found to increase the hazard of relapse to alcohol use ($p < 0.05$).

Discussion of Findings

The primary literature reviewed present limited evidence that cannabis use affects the rates and patterns of the use of other substances. With regard to alcohol use, cannabis users were found to be at a higher risk for heavy drinking than nonusers. With regard to opioids, cannabis use predicted continued opioid prescriptions 1 year after injury. Finally, cannabis use was associated with reduced odds of achieving abstinence from alcohol, cocaine, or polysubstance use after inpatient hospitalization and treatment for substance use disorders. The limitations of these studies include their lack of generalizability due to their use of restricted study populations, their limited assessment of cannabis use, the lack of dose–response relationships, and the potential for self-report bias.

CONCLUSION 14-2 There is limited evidence of a statistical association between cannabis use and changes in the rates and use patterns of other licit and illicit substances.

Is There an Association Between Cannabis Use and the Development of Other Substance Dependence or Other Substance Abuse Disorder?

Alcohol

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the development of alcohol dependence or alcohol use disorder.

Primary Literature Buu and colleagues (2014) assessed the long-term effects of cannabis use on alcohol problems and alcohol use disorder (AUD) using data from the Michigan Longitudinal Study. The researchers followed a sample of 160 female–male sibling pairs from high-risk families (sample total of 320 individuals) from ages 3–5 to 21–23 years, assessing the participants every 3 years using the Drinking and Drug History Questionnaire, Diagnostic Interview Schedule, Diagnostic Interview Schedule for Children, and the Health and Daily Living Questionnaire. Data were collected on age at first use of alcohol, cannabis, and nicotine as well as the quantity and frequency of use and were analyzed using a linear mixed model. The authors concluded that a higher frequency of cannabis use was related to greater odds of developing drinking problems (β , 0.55; SE = 0.08; $p < 0.05$) and to meeting an AUD diagnosis (β , 0.59; SE = 0.09; $p < 0.05$) (Buu et al., 2014). However, the odds were not as high as those associated with the frequency of alcohol consumption on the odds of developing drinking problems (β , 1.90; SE = 0.10; $p < 0.05$) and the odds of meeting an AUD diagnosis (β , 1.75; SE = 0.31; $p < 0.05$) (Buu et al., 2014). Furthermore, an early onset of cannabis use was not found to contribute to AUD. A major limitation of this study is that the participant population included children who had intact families in early childhood, families that were at high risk for developing AUD, and families of minority race/ethnicity, thus limiting the generalizability of the study results.

Tobacco/Nicotine

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the development of tobacco or nicotine dependence or tobacco or nicotine abuse disorder.

Primary Literature Timberlake and colleagues (2007) conducted a study to examine the role of cannabis use in adolescence and the likelihood of developing nicotine dependence and initiating daily tobacco smoking at an earlier age. Survey data were collected from 90,118 students participating in the National Longitudinal Study of Adolescent Health conducted in 132 U.S. schools (public and private) between September 1994 and April 1995. A subsample of participants was followed up at three points with more in-depth surveys, a baseline survey (Wave I), and two subsequent surveys (Wave II, 1 year after the baseline survey, and Wave III, 6 years later). Of these, 5,963 unrelated participants formed the primary sample and included individuals who had not smoked cigarettes by the baseline survey (Wave I) but smoked at least one cigarette by Wave III. Participants ranged in age from 18.3 to 27.7 years. Data on lifetime use of

cannabis and prior-month use at Wave I, age at daily cigarette smoking, and lifetime and current nicotine dependence at Wave III were available for these participants. A smaller sample of 1,447 participants who had tried cannabis by Wave I and for which data on the age of first use was available was used to examine lifetime and current nicotine dependence 6 years later. Cannabis use was classified as no lifetime use, experimental use (1–10 times), and regular use (greater than 10 times). Age at first use was also collected from adolescents who had experimented with cannabis by Wave I of the survey. Nicotine dependence was defined using the Fagerstrom Test for Nicotine Dependence. Demographic risk factor data were also collected. Survey-based logistic regression analysis and censored regression techniques were used to predict outcomes.

Results from this study indicate that regular lifetime users of cannabis at Wave I were 1.89 times more likely to develop lifetime nicotine dependence ($t = 2.3$ $p < 0.05$, adjusted odds ratio [aOR], 1.89; 95% CI = 1.09–3.30) than nonusers. Past-month users (both experimental and regular) at Wave I were 1.83 times more likely to develop lifetime nicotine dependence ($t = 2.3$ $p < 0.05$, aOR, 1.83; 95% CI = 1.08–3.11) than nonusers. Furthermore, lifetime users who began using at later ages (23–27) were less likely to develop nicotine dependence at Wave III compared to those who began using at earlier ages ($t = -3.3$ $p < 0.01$, aOR, 0.82; 95% CI = 0.73–0.93). Limitations associated with this study include self-reported data on substance use, and recall bias.

Agrawal and colleagues (2008), as described in the above section, studied women cannabis users and patterns of smoking and nicotine dependence. Survival analyses were used to examine whether women who smoked cannabis were at an increased risk of moving from regular smoker to nicotine dependent. After adjusting for covariates, the results indicate that women with a prior history of cannabis use were 2.8 times more likely (HR, 2.80; 95% CI = 1.84–4.26) to transition from regular smoking to nicotine dependence. Limitations associated with this study include the lack of generalizability to men, self-reported data on substance use, and recall bias.

Mixed Drug Use

Systematic Reviews The committee did not identify a good- or fair-quality systematic review that reported on the association between cannabis use and the development of substance dependence or substance abuse disorder.

Primary Literature In a longitudinal U.S. study of a nationally representative sample of 34,653 adults 18 years or older, Blanco and colleagues

TABLE 14-1 Cannabis Use in the Past 12 Months and Incident Psychiatric Disorders in Wave 2

Incident Psychiatric Disorders in Wave 2	Adjusted OR (95% CI)
Any substance use disorder (includes cannabis use disorder)	6.2 (4.1–9.4)
Any alcohol use disorder	2.7 (1.9–3.8)
Alcohol abuse	1.5 (1.1–2.0)
Alcohol dependence	1.9 (1.4–2.7)
Other drug use disorder	2.6 (1.6–4.4)
Other drug abuse	3.4 (2.5–5.4)
Other drug dependence	2.7 (1.6–4.5)
Nicotine dependence	1.7 (1.2–2.4)

NOTE: CI = confidence interval; OR = odds ratio.

SOURCE: Adapted from Blanco et al., 2016.

(2016) examined the association between cannabis use and the risk of developing substance abuse and other mental health disorders. This study investigated the potential association between cannabis use in the past year (Wave 1) with incident substance use disorders, alcohol abuse and dependence, other drug abuse and dependence, and nicotine dependence 3 years later (Wave 2). Both Wave 1 and Wave 2 adjusted for sociodemographic characteristics, a family history of substance use disorder, a disturbed family environment, childhood parental loss, low self-esteem, social deviance, education, recent trauma, past and present psychiatric disorders, and the respondent's history of divorce. The researchers found that, after adjusting for covariates, cannabis use in the 12 months preceding the interview was associated with an increased risk of developing any substance use disorders, including Cannabis Use Disorder (OR, 6.2; 95% CI = 4.1–9.4) (Blanco et al., 2016). The adjusted ORs for all incident psychiatric disorders in Wave 2 are presented in Table 14-1.

The frequency of cannabis use in Wave 1 was also associated with an incidence of any substance use disorder in Wave 2 (aOR, 1.9; 95% CI = 1.7–2.1), indicating a dose–response association between cannabis use and substance use disorder.² Some of the limitations of this study included the fact that substance use was ascertained by self-report, that there was a possibility of residual confounding, and that the follow-up period was limited to 3 years (Blanco et al., 2016).

Palmer and colleagues (2009) analyzed the substance use experiences

² Frequency of cannabis use was measured as “no use,” “some use but less than one use per month,” and “one or more uses per month.”

of 1,733 individuals (ages 12–25) who participated in the Colorado Community Twin Study. Data on substance use experimentation and repeated use were collected via self-reported questionnaires and psychiatric interviews in two waves about 5 years apart. Substance abuse and dependence were assessed using the Composite International Diagnostic Interview–Substance Abuse Module (CIDI–SAM) structured interview. With respect to substance use, experimentation was defined as “having used a substance one or more times in a person’s lifetime”; repeated marijuana use was defined as having used cannabis “six or more times in a respondent’s lifetime”; and cannabis abuse and dependence were defined based on the DSM-IV as having compulsive use without generally developing physiological dependence (APA, 1994, p. 216; Palmer et al., 2009, pp. 79–80).

Results show that the risks of alcohol abuse/dependence (OR, 3.44; 95% CI = 1.93–6.12) and tobacco dependence (OR, 4.12; 95% CI = 2.26–7.51) were greater in individuals who used cannabis more than once in their lifetime (without meeting a diagnosis of cannabis substance use disorder) compared to those who did not use cannabis (Palmer et al., 2009). Individuals diagnosed with cannabis use disorder had higher odds of being diagnosed with alcohol abuse/dependence (OR, 8.78; 95% CI = 3.15–24.53) and tobacco dependence (OR, 8.61; 95% CI = 3.15–23.56) than those who did not use cannabis. However, once the logistic regression models were adjusted for the individuals’ involvement with alcohol and tobacco, the ORs no longer reached significance (Palmer et al., 2009).

The researchers found that individuals with cannabis use disorder were not at higher risk for alcohol abuse/dependence (OR, 1.77; 95% CI = 0.54–5.78) or tobacco dependence (OR, 2.61; 95% CI = 0.78–8.72) compared with those who had used cannabis more than once in their lifetime but did not have cannabis use disorder (Palmer et al., 2009). They note that the cannabis and other substance use results indicate “a model of generalized risk since substance use disorders on any substance in young adulthood could be predicted by involvement with any of the three substances in adolescence” (Palmer et al., 2009, p. 78). Study limitations include the difficulty capturing the more severe cases in the cohort, as they are generally not reported; questions about the reliability of self-reporting; of the fact that covariates of substance abuse were not included in the logistic regression models; and the failure of the authors to impose clustering criteria or to distinguish between dependence with or without physiological symptoms (Palmer et al., 2009).

Using data from 1,265 participants of the Christchurch Health and Development longitudinal birth cohort study, Fergusson and colleagues (2008) explored factors associated with illicit drug use, abuse, or dependence among study participants at ages 16 to 25. Cannabis use data were collected for each year and were classified into four levels of frequency:

“did not use cannabis,” “used less than monthly on average (1–11 times),” “used at least monthly on average (12–50 times),” and “used at least weekly (>50 times)” (Fergusson et al., 2008, p. 169). Annual frequency of cannabis use was the strongest predictor of illicit drug use (β , 1.58; SE = 0.06, $p < 0.0001$) and drug abuse or dependence (β , 1.73; SE = 12, $p < 0.0001$) across age groups (Fergusson et al., 2008). The interaction between cannabis use and age was also explored and the association was found to diminish with increasing age. The adjusted odds ratios for the risk of illicit drug use and abuse/dependence for participants who used cannabis at least weekly are presented in Table 14-2 below. Study limitations include questions about the generalizability of the study and the fact that the assessments were based on self-reported data. The confidence intervals for some results are wide.

Discussion of Findings

Most of the studies reviewed indicate an association between cannabis use and use of or dependence on other substances, with some data indicating this effect is more pronounced in younger individuals and is dependent on the dose or frequency of cannabis use. The strengths of some studies cited include the study designs (longitudinal cohort stud-

TABLE 14-2 Adjusted Odds Ratios (and 95% Confidence Intervals) for at Least Weekly Cannabis Use and Risk Factors for Cannabis Use and Illicit Drug Abuse/Dependence, at Ages 16–17, 20–21, and 24–25

Adjusted Odds Ratios for at Least Weekly Frequency of Use of Cannabis and the Risk of Illicit Drug Use at Specific Ages		
Age	aOR	95% CI
16–17	92.20	46.53–182.72
20–21	26.31	17.50–39.69
24–25	7.53	4.48–12.43
Adjusted Odds Ratios for at Least Weekly Frequency of Use of Cannabis and Risk of Illicit Drug Abuse/Dependence		
16–17	117.92	26.31–523.74
20–21	27.61	11.24–67.90
24–25	6.49	2.19–19.20

NOTE: CI = confidence interval; aOR = adjusted odds ratio.

SOURCE: Adapted from Fergusson et al., 2008.

ies), the existence of large sample sizes, and the fact that adjustments were made for a variety of confounders. The magnitude of the associations appears in the moderate range. The limitations of the studies include, in most cases, the use of self-report for cannabis use, recall bias, and, in some cases, the limited duration of follow-up.

CONCLUSION 14-3 There is moderate evidence of a statistical association between cannabis use and the development of substance dependence and/or a substance abuse disorder for substances, including alcohol, tobacco, and other illicit drugs. The development of problem cannabis use is described in Chapter 13 of this report.

RESEARCH GAPS

To address the research gaps relevant to cannabis use and the abuse of other substances, the committee suggests the following:

- Additional studies are needed to determine whether cannabis use is an independent risk factor for, or causally contributes to, the initiation or use of and dependence on other drugs of abuse later in life.
- In states with legalized recreational cannabis, there need to be longitudinal studies that examine whether the prevalence of use of other drugs parallels the increase in prevalence of cannabis use.

SUMMARY

This chapter summarizes current research evidence on the association between cannabis use and the potential for abusing other substances. Several important research conclusions were reached (see Box 14-1); however, it is important that these conclusions be interpreted within the context of the limitations discussed in the Discussion of Findings sections above.

BOX 14-1
Summary of Chapter Conclusions*

There is moderate evidence of a statistical association between cannabis use and:

- The development of substance dependence and/or a substance abuse disorder for substances, including alcohol, tobacco, and other illicit drugs (14-3)

There is limited evidence of a statistical association between cannabis use and:

- The initiation of tobacco use (14-1)
- Changes in the rates and use patterns of other licit and illicit substances (14-2)

* Numbers in parentheses correspond to chapter conclusion numbers.

REFERENCES

- Agrawal, A., P. A. F. Madden, K. K. Bucholz, A. C. Hewath, and M. T. Lynskey. 2008. Transitions to regular smoking and to nicotine dependence in women using cannabis. *Drug and Alcohol Dependence* 95(1-2):107-114.
- Aharonovich, E., X. Liu, S. Samet, E. Nunes, R. Waxman, and D. Hasin. 2005. Postdischarge cannabis use and its relationship to cocaine, alcohol, and heroin use: A prospective study. *American Journal of Psychiatry* 162(8):1507-1514.
- APA (American Psychiatric Association). 1994. *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*. Washington, DC: American Psychiatric Association.
- Blanco, C., D. S. Hasin, M. M. Wall, L. Florez-Salamanca, N. Hoertel, S. Wang, B. T. Kerridge, and M. Olfson. 2016. Cannabis use and risk of psychiatric disorders: Prospective evidence from a U.S. national longitudinal study. *JAMA Psychiatry* 73(4):388-395.
- Buu, A., A. Dabrowska, M. Mygrants, L. I. Puttler, J. M. Jester, and R. A. Zucker. 2014. Gender differences in the developmental risk of onset of alcohol, nicotine, and marijuana use and the effects of nicotine and marijuana use on alcohol outcomes. *Journal of Studies on Alcohol and Drugs* 75(5):850-858.
- Buu, A., A. Dabrowska, J. E. Heinze, H. F. Hsieh, and M. A. Zimmerman. 2015. Gender differences in the developmental trajectories of multiple substance use and the effect of nicotine and marijuana use on heavy drinking in a high-risk sample. *Addictive Behaviors* 50:6-12.
- CBHSQ (Center for Behavioral Health Statistics and Quality). 2015. *Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health*. U.S. Department of Health and Human Services, Publication No. SMA 15-4927, NSDUH Series H-50. <http://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf> (accessed November 25, 2016).

- Fergusson, D. M., J. M. Boden, and L. J. Horwood. 2008. The developmental antecedents of illicit drug use: Evidence from a 25-year longitudinal study. *Drug and Alcohol Dependence* 96(1–2):1–2.
- IOM (Institute of Medicine). 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC: National Academy Press.
- Kandel, D. 1975. Stages in adolescent involvement in drug use. *Science* 190:912–914.
- Mayet, A., S. Legleye, N. Chau, and B. Falissard. 2011. Transitions between tobacco and cannabis use among adolescents: A multi-state modeling of progression from onset to daily use. *Addictive Behaviors* 36(11):1101–1105.
- Mayet, A., S. Legleye, F. Beck, B. Falissard, and N. Chau. 2016. The gateway hypothesis, common liability to addictions or the route of administration model: A modelling process linking the three theories. *European Addiction Research* 22(2):107–117.
- Novins, D. K., and A. E. Barón. 2004. American Indian substance use: The hazards for substance use initiation and progression for adolescents aged 14 to 20 years. *Journal of the American Academy of Child & Adolescent Psychiatry* 43(3):316–324.
- Palmer, R. H., S. E. Young, C. J. Hopfer, R. P. Corley, M. C. Stallings, T. J. Crowley, and J. K. Hewitt. 2009. Developmental epidemiology of drug use and abuse in adolescence and young adulthood: Evidence of generalized risk. *Drug and Alcohol Dependence* 102(1–3):1–3.
- Panlilio, L. V., Z. Justinova, P. Mascia, M. Pistis, A. Luchicchi, S. Lecca, C. Barnes, G. H. Redhi, J. Adair, S. J. Heishman, S. Yasar, M. Aliczki, J. Haller, and S. R. Goldberg. 2012. Novel use of a lipid-lowering fibrate medication to prevent nicotine reward and relapse: Preclinical findings. *Neuropsychopharmacology* 37:1838–1847.
- Patton, G. C., C. Coffey, M. T. Lynskey, S. Reid, S. Hemphill, J. B. Carlin, and W. Hall. 2007. Trajectories of adolescent alcohol and cannabis use into young adulthood. *Addiction* 102(4):607–615.
- Secades-Villa, R., O. Garcia-Rodriguez, C. J. Jin, S. Wang, and C. Blanco. 2015. Probability and predictors of the cannabis gateway effect: A national study. *Journal of Drug Policy* 26(2):135–142.
- Timberlake, D. S., B. C. Haberstick, C. J. Hopfer, J. Brickerm, J. R. Sakai, J. M. Lessem, and J. K. Hewitt. 2007. Progression from marijuana use to daily smoking and nicotine dependence in a national sample of U.S. adolescents. *Drug and Alcohol Dependence* 88(2–3):272–281.
- Vanyukov, M. M., R. E. Tarter, G. P. Kirillova, L. Kirisci, M. D. Reynolds, M. J. Kreek, K. P. Conway, B. S. Maher, W. G. Iacono, L. Bierut, M. C. Neale, D. B. Clark, and T. A. Ridenour. 2012. Common liability to addiction and “gateway hypothesis”: Theoretical, empirical and evolutionary perspective. *Drug and Alcohol Dependence* 123(Suppl 1):S3–S17.
- Whiteside, L. K., J. Russo, J. Wang, M. L. Ranney, V. Neam, and D. F. Zatzick. 2016. Predictors of sustained prescription opioid use after admission for trauma in adolescents. *Journal of Adolescent Health* 58(1):92–97.

Part IV

Research Barriers and Recommendations

15

Challenges and Barriers in Conducting Cannabis Research

Several states have legalized cannabis for medical or recreational use since the release of the 1999 Institute of Medicine (IOM)¹ report *Marijuana and Medicine: Assessing the Science Base* (IOM, 1999). As of October 2016, 25 states and the District of Columbia had legalized the medical use of cannabis, while 4 states and the District of Columbia had also legalized recreational cannabis use (NCSL, 2016; NORML, 2016a).² In November 2016, voters in California, Maine, Massachusetts, and Nevada approved ballot initiatives to legalize recreational cannabis, while voters in Arkansas, Florida, Montana, and North Dakota approved ballot initiatives to permit or expand the use of cannabis for medical purposes (NORML, 2016b).

Policy changes are associated with marked changes in patterns of cannabis use. In recent years, the number of U.S. adolescents and adults ages 12 and older who reported using cannabis increased by 35.0 percent and 20.0 percent for use in the past month and in the past year, respectively (Azofeifa et al., 2016). Revenue from the sale and taxation of cannabis can serve as a proxy measure for cannabis use and suggests that the scope of cannabis use in the United States is considerable. For example, the total estimated value of legal cannabis sales in the United States was \$5.7 bil-

¹ As of March 2016, the Health and Medicine Division continues the task of producing consensus studies and convening activities previously undertaken by the Institute of Medicine (IOM).

² The count of states where cannabis is legalized for medical use includes Ohio and Pennsylvania, where medical cannabis laws were not operational as of October 2016 (NCSL, 2016).

lion in 2015 and \$7.1 billion in 2016 (Arcview Market Research and New Frontier Data, 2016). At the state level, the Colorado Department of Revenue reported that sales and excise taxes on recreational and medical cannabis sales totaled \$88,239,323 in fiscal year 2015 (CDOR, 2016a, p. 29),³ and in Washington, state and local sales taxes and state business and occupation taxes on recreational and medical cannabis totaled \$53,410,661 in fiscal year 2016 (WDOR, 2016a,b).⁴

Despite these changes in state policy and the increasing prevalence of cannabis use and its implications for population health, the federal government has not legalized cannabis and continues to enforce restrictive policies and regulations on research into the health harms or benefits of cannabis products that are available to consumers in a majority of states. As a result, research on the health effects of cannabis and cannabinoids has been limited in the United States, leaving patients, health care professionals, and policy makers without the evidence they need to make sound decisions regarding the use of cannabis and cannabinoids. This lack of evidence-based information on the health effects of cannabis and cannabinoids poses a public health risk.

In order to promote research on cannabis and cannabinoids, the barriers to such research must first be identified and addressed. The committee identified several barriers to conducting basic, clinical, and population health research on cannabis and cannabinoids, including regulations and policies that restrict access to the cannabis products that are used by an increasing number of consumers and patients in state-regulated markets, funding limitations, and numerous methodological challenges. The following sections discuss these barriers in detail.

REGULATORY AND SUPPLY BARRIERS

Regulatory Barriers

Investigators seeking to conduct research on cannabis or cannabinoids must navigate a series of review processes that may involve the National Institute on Drug Abuse (NIDA), the U.S. Food and Drug Administration (FDA), the U.S. Drug Enforcement Administration (DEA), institutional review boards, offices or departments in state government, state boards

³ \$22,225,750 (Marijuana Sales Tax [2.9%]) + \$42,017,798 (Retail Marijuana Sales Tax [10%]) + \$23,995,775 (Retail Marijuana Excise Tax [15%]) = \$88,239,323.

⁴ Medical Cannabis: \$5,236,536 (State Retail Sales Tax) + \$792,906 (State Business and Occupation Tax) + \$ 2,084,323 (Local Retail Sales Tax) = \$8,113,765. Recreational Cannabis: \$30,017,823 (State Retail Sales Tax) + \$4,050,212 (State Business & Occupation Tax) + \$11,228,861 (Local Retail Sales Tax) = \$45,296,896. \$8,113,765 (Total Medical Cannabis Taxes) + \$45,296,896 (Total Recreational Cannabis Taxes) = \$53,410,661.

of medical examiners, the researcher's home institution, and potential funders. A brief overview of some of these review processes is discussed.

Researchers conducting clinical research on biological products such as cannabis must submit an investigational new drug (IND) application to the FDA. As a next step, the investigator may contact NIDA, an important source of research-grade cannabis, to obtain an administrative letter of authorization (LOA). An LOA describes the manufacturer's facilities, as well as the availability and pertinent characteristics of the desired cannabis product (e.g., strains, quality, strength, pharmacology, toxicology). To safeguard against the acquisition of cannabis or cannabinoids for non-research purposes, investigators must also apply for a DEA registration and site licensure before conducting studies involving cannabis or any of its cannabinoid constituents, irrespective of their pharmacologic activity.⁵ The investigator must submit the IND and LOA to the FDA and the DEA for review (FDA, 2015).

After submitting an IND application, researchers must wait at least 30 days before initiating research, during which period the FDA reviews the application to ensure that research participants will not be exposed to unreasonable risk (FDA, 2016a). If the FDA determines that the proposed research would expose study participants to unreasonable risk or that the IND application is in some other way deficient, a clinical hold postponing the research may be imposed. This hold is not lifted until and unless the sponsoring researchers have resolved the deficiencies (FDA, 2016b).

It is important to note that the Controlled Substances Act of 1970 classified cannabis as a Schedule I substance, the highest level of drug restriction.⁶ As defined by the Act, Schedule I substances are those that (1) have a high potential for abuse; (2) have no currently accepted medical use in treatment in the United States; and (3) have a lack of accepted safety for their use under medical supervision.⁷ Other substances classified in Schedule I include heroin, LSD, mescaline, hallucinogenic amphetamine derivatives, fentanyl derivatives (synthetic opioid analgesics), and gamma-hydroxybutyrate (GHB).⁸ By contrast, Schedule II substances—though they also have a high potential for abuse and may lead to severe psychological or physical dependence—are defined as having a currently

⁵ Code of Federal Regulations, Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances, Title 21, § 1301.11 and Code of Federal Regulations, Schedules of Controlled Substances, Title 21, § 1308.11.

⁶ Code of Federal Regulations, Schedules of Controlled Substances, Title 21, § 1308.11; United States Code, Schedules of Controlled Substances, Title 21, § 812.

⁷ United States Code, Schedules of Controlled Substances, Title 21, § 812(b)(1).

⁸ Code of Federal Regulations, Schedules of Controlled Substances, Title 21, § 1308.11.

BOX 15-1
Illustrative Examples of the Current Research
Barriers to Colorado Researchers

As a concrete example of the impact of the divide between federal and state policy, cannabis concentrate sales doubled in Colorado from 2015 to 2016, reaching \$60.5 million in the first quarter of 2016 (Marijuana Business Daily Staff, 2016), and yet current federal law prevents chemists from examining the composition of those products as it may relate to safety, neuroscientists from testing the effects of those products on the brain or physiology in animal models, and clinical scientists from conducting research on how these products may help or harm patients. And while between 498,170 and 721,599 units of medical and recreational cannabis edibles were sold per month in Colorado in 2015 (CDOR, 2016b, p. 12), federal law also prohibits scientists from testing those products for contaminants, understanding the effects of these products in animal models, or investigating the effects in patient populations.

accepted medical use and can be prescribed with a controlled substance prescription (DEA, 2006).⁹

In some states, researchers conducting clinical research on cannabis or cannabinoid products must also apply for and receive a controlled substance certificate from a state board of medical examiners or a controlled substance registration from a department of the state government in order to conduct clinical trials or any other activity involving Schedule I substances (Alabama Board of Medical Examiners, 2013; MDHSS, n.d.). Some state governments require additional approvals. For example, California requires that all trials involving Schedule I or II controlled substances be registered with and approved by the Research Advisory Panel of California (CADOJ/OAG, 2016). When the necessary approvals are secured, only then can the investigator apply for a DEA registration and site licensure to conduct research on a Schedule I controlled substance (see Box 15-1 for examples of research barriers).

Researchers conducting trials of Schedule I substances must additionally submit a research protocol to the DEA that includes details regarding the security provisions for storing and dispensing the substance.¹⁰ Previously, nonfederally funded studies on cannabis were also required to undergo an additional review process conducted by the Public Health

⁹ United States Code, Schedules of Controlled Substances, Title 21, § 812(b)(2).

¹⁰ Code of Federal Regulations, Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances, Title 21, § 1301.18.

Service. This review process was determined to unnecessarily duplicate the FDA's IND application process in several ways and, as of June 2015, is no longer required.¹¹

To ensure that controlled substances obtained for research purposes will be stored and accessed in accordance with DEA security requirements, local DEA officials may perform a preregistration inspection of the facility where the proposed research will take place (University of Colorado, 2016). DEA security requirements include storing cannabis in a safe, a steel cabinet, or a vault, and limiting access to the storage facility to "an absolute minimum number of specifically authorized employees."¹² The extent of the security measures required by DEA varies with the amount of cannabis being stored,¹³ and among local DEA jurisdictions (Woodworth, 2011). Funders must bear the costs of meeting the necessary security requirements.

Additionally, as with any human clinical trial, approval from an institutional review board must be sought.¹⁴ Obtaining this approval confirms that an appropriate plan to protect the rights and welfare of human research subjects has been outlined in the proposed research efforts. If a study is being conducted in a clinical research center, a separate review may be required by this entity's medical or research advisory committee.

In summary, basic and clinical researchers seeking to obtain cannabis or cannabinoids from NIDA for research purposes—including efforts to determine the value of cannabis or cannabinoids for treating a medical condition or achieving a therapeutic end need—must obtain a number of approvals from a range of federal, state, or local agencies, institutions, or organizations. This process can be a daunting experience for researchers. The substantial layers of bureaucracy that emerge from cannabis's Schedule I categorization is reported to have discouraged a number of cannabis researchers from applying for grant funding or pursuing additional research efforts (Nutt et al., 2013). Given the many gaps in the research of the health effects of cannabis and cannabinoids, there is a need to address these regulatory barriers so that researchers will be

¹¹ Office of the Secretary, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services. Notice. "Announcement of Revision to the Department of Health and Human Services Guidance on Procedures for the Provision of Marijuana for Medical Research as Published on May 21, 1999," *Federal Register*, 80, no. 120 (June 23, 2015): 35960, <https://www.gpo.gov/fdsys/pkg/FR-2015-06-23/pdf/2015-15479.pdf> (accessed November 25, 2016).

¹² Code of Federal Regulations, Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances, Title 21, § 1301.72 (a) and (d).

¹³ Code of Federal Regulations, Registration of Manufacturers, Distributors, and Dispensers of Controlled Substances, Title 21, § 1301.71 (c).

¹⁴ Code of Federal Regulations, Institutional Review Boards, Title 21, § 56.103.

better able to address key public health questions about the therapeutic and adverse effects of cannabis and cannabinoid use.

CONCLUSION 15-1 There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research.¹⁵

Barriers to Cannabis Supply

In the United States, cannabis for research purposes is available only through the NIDA Drug Supply Program (NIDA, 2016a). The mission of NIDA is to “advance science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health,” rather than to pursue or support research into the potential therapeutic uses of cannabis or any other drugs (NIDA, 2016b). As a result of this emphasis, less than one-fifth of cannabinoid research funded by NIDA in fiscal year 2015 concerns the therapeutic properties of cannabinoids (NIDA, 2016c).¹⁶ Because NIDA funded the majority of all the National Institutes of Health (NIH)-sponsored cannabinoid research in fiscal year 2015 (NIDA, 2016c),¹⁷ its focus on the consequences of drug use and addiction constitutes an impediment to research on the potential beneficial health effects of cannabis and cannabinoids.

All of the cannabis that NIDA provides to investigators is sourced from the University of Mississippi, which is currently the sole cultivator of the plant material and has been since 1968 (NIDA, 1998, 2016a).¹⁸ In the past, the varieties of cannabis that were available to investigators through NIDA were limited in scope and were not of comparable potency to what patients could obtain at their dispensaries (Stith and Vigil, 2016). Because

¹⁵ The committee was specifically directed in its statement of task not to comment on cannabis policy issues, such as regulatory options for legalization, taxation, or distribution. While the committee has identified the Schedule 1 classification of cannabis as posing a significant barrier to the conduct of scientific research on the health effects of cannabis, the committee is aware that any decision on the regulation of cannabis involves many factors far outside the committee’s remit and expertise. Specifically, the committee did not comment on the abuse or dependency liability or accepted medical use of cannabis compared to other scheduled drugs.

¹⁶ In fiscal year 2015, NIDA’s investment in cannabinoid research totaled \$66,078,314, of which \$10,923,472 was allocated for therapeutic cannabinoid research (NIDA, 2016c).

¹⁷ In fiscal year 2015, NIH’s investment in cannabinoid research totaled \$ \$111,275,219, of which \$66,078,314 was allocated to NIDA (NIDA, 2016c).

¹⁸ NIDA contracts with the University of Mississippi through an open solicitation process. Although the University of Mississippi is currently NIDA’s only supplier of research-grade cannabis, other groups can compete for the contract (NIDA, 2015, 2016a).

of restrictions on production and vicissitudes in supply and demand, federally produced cannabis may have been harvested years earlier, is stored in a freezer (a process that may affect the quality of the product) (Taschwer and Schmid, 2015; Thomas and Pollard, 2016), and often has a lower potency than cannabis sold in state-regulated markets (Reardon, 2015; Stith and Vigil, 2016). In addition, many products available in state-regulated markets (e.g., edibles, concentrates, oils, wax, topicals) are not commonly available through federal sources (NIDA, 2016d). Since the products available through the federal system do not sufficiently reflect the variety of products used by consumers, research conducted using cannabis provided by NIDA may lack external validity. In July 2016, NIDA posted a formal request for information on the varieties of cannabis and cannabis products of interest to researchers (NIDA, 2016e). Reflecting the perceived shortcomings of cannabis and cannabis products currently provided by NIDA, a summary of the comments received in response to this request states that “the most consistent recommendation was to provide marijuana strains and products that reflect the diversity of products available in state dispensaries” (NIDA, 2016e).

Naturally, it is difficult for a single facility at the University of Mississippi to replicate the array and potency of products available in dispensaries across the country. It is worth noting, however, that NIDA has been increasingly responsive to the needs of clinical investigators. For example, NIDA has contracted with the University of Mississippi to produce cannabis strains with varying concentrations of Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD) (NIDA, 2016d), and NIDA has previously authorized development of cannabis extracts, tinctures, and other dosage formulations for research purposes (Thomas and Pollard, 2016). As mentioned above, NIDA has sought public comment on the needs of cannabis researchers in order to inform efforts to “expand access to diverse marijuana strains and products for research purposes” (NIDA, 2016e). In addition, cannabis is made available to research investigators funded by NIH at no cost.¹⁹ Finally, the DEA has adopted a new policy that increases the number of entities that may be registered under the Controlled Substances Act (CSA) to grow (manufacture) marijuana to supply legitimate researchers in the United States.²⁰ Under this new policy, the DEA will facilitate cannabis research by increasing the number of private

¹⁹ In December 2016, cannabis provided by NIDA was generally free for NIH-sponsored research. For research not funded by the federal government, the cost of non-placebo cannabis was \$10.96 per cigarette and \$1,133 per pound (\$2,497 per kilogram) (NIDA, 2016d).

²⁰ DEA, U.S. Department of Justice. Policy Statement. “Applications to Become Registered Under the Controlled Substances Act to Manufacture Marijuana to Supply Researchers in the United States,” *Federal Register*, 81, no. 156 (August 12, 2016): 53846, <https://www.gpo.gov/fdsys/pkg/FR-2016-08-12/pdf/2016-17955.pdf> (accessed January 7, 2017).

entities allowed to cultivate and distribute research-grade cannabis. As of December 2016, the University of Mississippi remains the sole cultivator of cannabis provided to researchers by NIDA (NIDA, 2016a).

Although new plans are being made to provide a wider array of more clinically relevant cannabis products for research, at present this issue is still a significant barrier for conducting comprehensive research on the health effects of cannabis use. How the proposed changes will affect cannabis research in the future remains to be seen.

CONCLUSION 15-2 It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use.

Funding Limitations

Funding for research is another key barrier; without adequate financial support, cannabis research will be unable to inform health care or public health practice or to keep pace with changes in cannabis policy and patterns of cannabis use. NIH is responsible for funding research across a number of health domains. In 2015, NIH spending on all cannabinoid research totaled \$111,275,219 (NIDA, 2016c). NIDA, a member institute of NIH, has as its mission to study factors related to substance abuse and dependence and conducts research on the negative health effects and behavioral consequences associated with the abuse of cannabis and other drugs (NIDA, 2016b). Because cannabis was historically perceived to have only negative effects, the majority of cannabis research has been conducted under the auspices of NIDA.

In fiscal year 2015, studies supported by NIDA accounted for 59.3 percent (\$66,078,314) of all NIH spending on cannabinoid research; however, only 16.5 percent (\$10,923,472) of NIDA's spending on cannabinoid research supported studies investigating therapeutic properties of cannabinoids (NIDA, 2016c).^{21,22} As demonstrated in Chapter 4 of this report, a growing body of evidence suggests that cannabis and cannabinoids also have therapeutic health effects. In light of these findings, a comprehen-

²¹ $\$66,078,314$ (Total NIDA spending on cannabinoid research in fiscal year 2015) / $\$111,275,219$ (Total NIH spending on cannabinoid research in fiscal year 2015) = 0.593. $\$10,923,472$ (Total NIDA spending on therapeutic cannabinoid research in fiscal year 2015) / $\$66,078,314$ (Total NIDA spending on cannabinoid research in fiscal year 2015) = 0.165.

²² By contrast, NIH spending on tobacco research totaled \$300 million in 2015, and spending on research related to the harms and benefits of alcohol use totaled \$473 million in 2015 (NIH, 2016).

sive research agenda that investigates both the potential adverse and the potential therapeutic health effects of cannabis use is needed.

However, it may be unrealistic to expect NIDA to have the resources or interest to fund this broader research agenda, which could involve investigating the health effects of cannabis use on a diverse range of conditions (e.g., metabolic syndrome, cardiovascular disease, cancer, obesity and sedentary behavior, Alzheimer's disease) that are targeted by other institutes and centers of NIH. While it is not clear how these studies might be funded, almost assuredly the changing norms and the changing legal status of cannabis will have an impact on conditions that are targeted by institutes other than NIDA, and it will become increasingly important to have a funding mechanism to better understand the comprehensive health effects of cannabis so that consumers and policy makers can respond to changing trends accordingly.

CONCLUSION 15-3 A diverse network of funders is needed to support cannabis and cannabinoid research that explores the harmful and beneficial health effects of cannabis use.

METHODOLOGICAL CHALLENGES

Drug Delivery Challenges

Another challenge in investigating the potential health effects of cannabis and cannabinoids is the identification of a method of administering the drug that is accepted by study participants, that can be performed at most research sites, and that ensures standardized dosing. Smoking as a route of administration is particularly challenging, as some study participants may not view it as an acceptable method of drug administration, and academic medical centers or other locations where cannabis or cannabinoid research takes place may lack facilities where study participants can smoke under controlled conditions. Furthermore, variations among individuals in terms of their cannabis smoking techniques make it difficult to ensure that study participants reliably receive the targeted dose of the drug. Devices for providing a metered dose of cannabis via inhalation exist (Eisenberg et al., 2014), but the FDA has not approved such devices for use. Standardized smoking techniques have also been developed (Foltin et al., 1988) but can be difficult to perform correctly. These difficulties are due, in part, to differences among individuals in their tolerance of the potential psychoactive effects of the drug (D'Souza et al., 2008; Ramaekers et al., 2009), which may prevent the receipt of equal doses by all study participants.

Researchers have also explored vaporization as a method for adminis-

tering cannabis (Abrams et al., 2007). Cannabinoids vaporize at lower temperatures than the temperature at which pyrolytic toxic compounds are created through combustion; as a result, levels of some carcinogenic compounds are lower in cannabis vapor than in cannabis smoke (Eisenberg et al., 2014). However, there is a paucity of research on the effectiveness of these devices as a mode of drug administration. For example, data on the plasma concentrations of cannabinoids achieved through use of vaporizers exists, but they are limited (Abrams et al., 2007; Zuurman et al., 2008). In addition, even less is known about the long-term pulmonary effects of inhaling a vaporized liquid than about the effect of inhaling plant material. As vaporizing devices proliferate and evolve, researchers may benefit from advances in their portability and usability, but they will also have to account for clinically relevant differences in the functioning and the effectiveness of an increasingly wide range of models.

To circumvent the practical and methodological challenges involved in administration of cannabis through smoking or vaporization, investigators may choose to study the health effects of orally administered dronabinol or nabilone, which offer a more controlled method of drug delivery. However, the effects generated by these isolated cannabinoids might, at least in part, be different from those produced by the use of the whole cannabis plant, which also contains CBD and other cannabinoids, as well as terpenoids and flavonoids. As a result, extrapolating from the observed health effects associated with use of an isolated cannabinoid such as dronabinol or nabilone in order to predict the health effects associated with the use of cannabis may lead to erroneous conclusions.

The Placebo Issue

The gold standard of drug development is the prospective, randomized, double-blind, placebo-controlled clinical trial. Placebo cannabis produced by solvent extraction is available from NIDA and has a potency of 0.002 percent THC by weight and 0.001 percent CBD by weight (NIDA, 2016d).²³ The extraction process seems to retain the terpenoids and flavonoids so that the combusted placebo material smells similar to the true cannabis, thus helping to preserve the blinding to some extent. However, the psychoactive and vasoactive effects of cannabis pose a considerable challenge for effective blinding, since study participants who feel such

²³ In December 2016, placebo cannabis provided by NIDA was generally free for NIH-sponsored research. For research not funded by the federal government, the cost of placebo cannabis was \$13.94 per cigarette and \$1,133 per pound (\$2,497 per kilogram) (NIDA, 2016d).

effects will surmise that they are receiving cannabis or cannabinoids, and not a placebo.

Strategies to promote the effectiveness of blinding exist. For example, if the cannabis being studied has a very low THC content, study participants—especially those who, through regular use of more potent cannabis strains, are inured to the psychoactive effects of cannabis with low THC content—may not notice the psychoactive effects of the cannabis and therefore be unable to reliably determine whether they are using cannabis or a placebo. There is also a possibility that cannabis products with a lower ratio of the concentration of THC to the concentration of CBD may have less psychoactivity than products with a comparatively higher ratio of the concentration of THC to the concentration of CBD (Hindocha et al., 2015; Jacobs et al., 2016). Using these strains with diminished psychoactive effects could promote more effective blinding. Researchers may also try treating both study arms in a placebo-controlled cannabis trial with a mildly psychoactive or sedating drug, the effects of which may help to ensure that study participants are unable to determine whether they are receiving a placebo or cannabis. However, by introducing another active agent, the investigators risk obfuscating the results of their study.

A potential method for assessing the effectiveness of blinding in a cannabis trial is to ask study participants to guess whether they are receiving true cannabis or a placebo. If most or all of the participants correctly guess their assignment, it can be inferred that the blinding was ineffective. Whether or not such methods are employed, investigators risk undermining their study results. On the one hand, conducting the test carries the risk of discovering that attempts at blinding were ineffective, thereby rendering the study results invalid. On the other hand, not conducting the test may lead journal reviewers aware of the challenges of blinding in cannabis trials to assume that blinding was ineffective and to discount the study results accordingly. Thus, research to address the challenge of achieving reliably effective blinding in a cannabis trial is of marked importance.

Exposure Assessment

In order to arrive at valid and meaningful results, population studies on the health effects of cannabis require as detailed an ascertainment of exposure to cannabis as possible. However, obtaining such a detailed exposure history can be difficult. This is especially true for recreational cannabis use due to the lack of a standardized dose and the existence of diverse routes of administration, including multiple modes of inhalation (Schauer et al., 2016). In addition, known pharmacological biomarkers of cannabis use may be unreliable in some circumstances, while population

studies to identify novel pharmacological biomarkers of cannabis exposure are limited (Hartman et al., 2016; Schwoppe et al., 2011). Furthermore, the wide variety of different cannabis strains developed through a long and ongoing process of cultivation and the associated variation in the concentration of active substances in cannabis further complicate the characterization of cannabis exposure (ElSohly and Gul, 2014; Elsohly et al., 2016; Mehmedic et al., 2010). Finally, recreational cannabis may contain chemical contaminants or adulterants (Busse et al., 2008). Cannabis users may be unaware of the presence of these chemicals, making it unlikely that such chemicals would be identified through toxicological evaluation unless the user became involved in a forensic investigation.

Most observational studies, particularly case-control and cohort studies, depend on self-report in order to assess cannabis exposure. These reports may be incomplete, inaccurate, or imprecise due to failure on the part of investigators to ask cannabis users detailed questions about their cannabis exposure history, including the source of their cannabis exposure (e.g., smoking, edibles, vaping), or because users themselves may have limited knowledge of some aspects of their exposure or may be resistant to reporting some information. Personal recall of substance use may also be affected by other factors. For example, memory problems have been identified as a cause of inaccuracies in reporting drug use (Johnson and Fendrich, 2005; Pedersen, 1990). In other cases, study participants may not report illicit substance use in an attempt to conform to perceived social norms (Johnson and Fendrich, 2005). Similarly, individuals with substance dependency syndromes may have psychiatric comorbidity that affects the accuracy of reporting.

Finally, important information often missing from cannabis exposure histories is the extent of other substance use. As noted in Chapter 14, there is limited evidence that cannabis use is associated with the use of other licit or illicit substances. Despite this association and the confounding effect of polysubstance use on evaluations of the health effects of cannabis use, surveys used to characterize cannabis exposure histories do not always assess for the presence of other substance use. Since secondhand exposure to cannabis smoke can have minor health effects, there may also be value in assessing for such exposure as part of larger assessments of cannabis exposure (Herrmann et al., 2015).

Cannabis-Related Study Designs

In researching the health outcomes of cannabis use, the committee identified a number of studies, particularly cohort studies, of general health outcomes such as all-cause mortality or important chronic illnesses such as cancers or cardiovascular diseases. For both cohort and

case-control studies, a better assessment of cannabis use would offer more valuable information, such as years of use and age at first use. Particularly for cohort studies, this would offer better ascertainment of the duration and net burden of use as well as more insight into period and age effects. As discussed in the proceeding health outcomes chapters of the report, in many of the existing cohort studies cannabis use was often queried only at baseline, and thus there was little information on interval use over time or on the variation or cessation in that use. There was also very limited information on interval health events as the cohorts progressed, impeding a summarization of long-term use and the consequent health effects. Attention to these issues will likely improve the precision of study findings.

CONCLUSION 15-4 To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed.

BOX 15-2
Summary of Chapter Conclusions*

There are several challenges and barriers in conducting cannabis and cannabinoid research, including

- There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research (15-1)
- It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use (15-2)
- A diverse network of funders is needed to support cannabis and cannabinoid research that explores the harmful and beneficial health effects of cannabis use (15-3)
- To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed (15-4)

* Numbers in parentheses correspond to chapter conclusion numbers.

SUMMARY

The methodological challenges and the regulatory, financial, and access barriers described above markedly affect the ability to conduct comprehensive basic, clinical, and public health research on the health effects of cannabis use, with further consequences for the many potential beneficiaries of such research. In the absence of an appropriately funded and supported cannabis research agenda, patients may be unaware of viable treatment options, providers may be unable to prescribe effective treatments, policy makers may be hindered from developing evidence-based policies, and health care organizations and insurance providers lack a basis on which to revise their care and coverage policies. In short, such barriers represent a public health problem. See Box 15-2 for a summary of the chapter conclusions.

REFERENCES

- Abrams, D. I., H. P. Vizoso, S. B. Shade, C. Jay, M. E. Kelly, and N. L. Benowitz. 2007. Vaporization as a smokeless cannabis delivery system: A pilot study. *Clinical Pharmacology & Therapeutics* 82(5):572–578.
- Alabama Board of Medical Examiners. 2013. Chapter 540-X-4: Controlled Substances Certificate in *Alabama Board of Medical Examiners Administrative Code*. <http://www.alabamaadministrativecode.state.al.us/docs/mexam/540-X-4.pdf> (accessed December 29, 2016).
- Arcview Market Research and New Frontier Data. 2016. *The State of Legal Marijuana Markets, 4th Edition: Executive Summary*. San Francisco, CA: The Arcview Group. <http://mjardin.com/wp-content/uploads/2016/05/Executive-Summary-State-of-Legal-Marijuana-Markets-4th-Edition-1.pdf> (accessed December 8, 2016).
- Azofeifa, A., M. E. Mattson, G. Schauer, T. McAfee, A. Grant, and R. Lyerla. 2016. National estimates of marijuana use and related indicators—National Survey on Drug Use and Health, United States, 2002–2014. *The Morbidity and Mortality Weekly Report Surveillance Summaries* 65(11):1–28.
- Busse, F., L. Omid, K. Timper, A. Leichtle, M. Windgassen, E. Kluge, and M. Stumvoll. 2008. Lead poisoning due to adulterated marijuana. *New England Journal of Medicine* 358(15):1641–1642.
- CADOJ/OAG (State of California Department of Justice/Office of the Attorney General). 2016. *Research Advisory Panel: Guidelines*. <https://oag.ca.gov/research/guide> (accessed November 3, 2016).
- CDOR (Colorado Department of Revenue). 2016a. *Annual Report 2015*. Denver: Colorado Department of Revenue. https://www.colorado.gov/pacific/sites/default/files/2015%20Annual%20Report_1.pdf (accessed December 8, 2016).
- CDOR. 2016b. *MED 2015 Annual Update*. Denver, CO: Colorado Department of Revenue. https://www.colorado.gov/pacific/sites/default/files/2015%20Annual%20Update%20FINAL%2009262016_1.pdf (accessed December 7, 2016).
- DEA (U.S. Drug Enforcement Administration). 2006. Section V: Valid Prescription Requirements. In *Practitioner’s Manual: An Informational Outline of the Controlled Substances Act*. Washington, DC: Drug Enforcement Administration. Pp. 18–22. https://www.deadiversion.usdoj.gov/pubs/manuals/pract/pract_manual012508.pdf (accessed December 28, 2016).

- D'Souza, D. C., M. Ranganathan, G. Braley, R. Gueorguieva, Z. Zimolo, T. Cooper, E. Perry, and J. Krystal. 2008. Blunted psychotomimetic and amnesic effects of delta-9-tetrahydrocannabinol in frequent users of cannabis. *Neuropsychopharmacology* 33(10):2505–2516.
- Eisenberg, E., M. Ogintz, and S. Almog. 2014. The pharmacokinetics, efficacy, safety, and ease of use of a novel portable metered-dose cannabis inhaler in patients with chronic neuropathic pain: A phase 1a study. *Journal of Pain & Palliative Care Pharmacotherapy* 28(3):216–225.
- ElSohly, M., and W. Gul. 2014. Chapter 5: The Chemical Phenotypes (Chemotypes) of Cannabis. In *Handbook of Cannabis*, edited by R. Pertwee. New York: Oxford University Press. Pp. 89–110.
- ElSohly, M. A., Z. Mehmedic, S. Foster, C. Gon, S. Chandra, and J. C. Church. 2016. Changes in cannabis potency over the last 2 decades (1995–2014): Analysis of current data in the United States. *Biological Psychiatry* 79(7):613–619.
- FDA (U.S. Food and Drug Administration). 2015. Marijuana research with human subjects. <http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm421173.htm> (accessed January 3, 2017).
- FDA. 2016a. Investigational New Drug (IND) Application: Introduction. <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm> (accessed December 8, 2016).
- FDA. 2016b. IND application procedures: Clinical hold. <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm362971.htm> (accessed December 8, 2016).
- Foltin, R., M. Fischman, and M. Byrne. 1988. Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. *Appetite* 25:577–582.
- Hartman, R. L., T. L. Brown, G. Milavetz, A. Spurgin, D. A. Gorelick, G. R. Gaffney, and M. A. Huestis. 2016. Effect of blood collection time on measured delta9-tetrahydrocannabinol concentrations: Implications for driving interpretation and drug policy. *Clinical Chemistry* 62(2):367–377.
- Herrmann, E. S., E. J. Cone, J. M. Mitchell, G. E. Bigelow, C. LoDico, R. Flegel, and R. Vandrey. 2015. Non-smoker exposure to secondhand cannabis smoke II: Effect of room ventilation on the physiological, subjective, and behavioral/cognitive effects. *Drug and Alcohol Dependence* 151:194–202.
- Hindocha, C., T. P. Freeman, G. Schafer, C. Gardener, R. K. Das, C. J. Morgan, and H. V. Curran. 2015. Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: A randomised, double-blind, placebo-controlled study in cannabis users. *European Neuropsychopharmacology* 25(3):325–334.
- IOM (Institute of Medicine). 1999. *Marijuana and medicine: Assessing the science base*. Washington, DC: National Academy Press.
- Jacobs, D. S., S. J. Kohut, S. Jiang, S. P. Nikas, A. Makriyannis, and J. Bergman. 2016. Acute and chronic effects of cannabidiol on delta(9)-tetrahydrocannabinol (delta(9)-THC)-induced disruption in stop signal task performance. *Experimental and Clinical Psychopharmacology* 24(5):320–330.
- Johnson, T., and M. Fendrich. 2005. Modeling sources of self-report bias in a survey of drug use epidemiology. *Annals of Epidemiology* 15(5):381–389.
- Marijuana Business Daily Staff. 2016. Chart of the Week: Sales of Marijuana Concentrates, Edibles Surging in Colorado. Marijuana Business Daily, June 13. <http://mjbizdaily.com/chart-of-the-week-sales-of-marijuana-concentrates-edibles-surging-in-colorado> (accessed December 29, 2016).

- Mehmedic, Z., S. Chandra, D. Slade, H. Denham, S. Foster, A. S. Patel, S. A. Ross, I. A. Khan, and M. A. ElSohly. 2010. Potency trends of delta9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. *Journal of Forensic Science* 55(5): 1209–1217.
- MDHSS (Missouri Department of Health and Senior Services). n.d. *Frequently Asked Questions*. <http://health.mo.gov/safety/bndd/faqs.php> (accessed December 29, 2016).
- NCSL (National Conference of State Legislatures). 2016. *State Medical Marijuana Laws*. <http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx> (accessed December 22, 2016).
- NIDA (National Institute on Drug Abuse). 1998. *Provision of Marijuana and Other Compounds for Scientific Research—Recommendations of the National Institute on Drug Abuse National Advisory Council*. <https://archives.drugabuse.gov/about/organization/nacda/MarijuanaStatement.html> (accessed December 29, 2016).
- NIDA. 2015. Information on Marijuana Farm Contract. <https://www.drugabuse.gov/drugs-abuse/marijuana/nidas-role-in-providing-marijuana-research/information-marijuana-farm-contract> (accessed December 29, 2016).
- NIDA. 2016a. NIDA's Role in Providing Marijuana for Research. <https://www.drugabuse.gov/drugs-abuse/marijuana/nidas-role-in-providing-marijuana-research> (accessed December 8, 2016).
- NIDA. 2016b. National Institute on Drug Abuse (NIDA): Mission. <https://www.nih.gov/about-nih/what-we-do/nih-almanac/national-institute-drug-abuse-nida> (accessed December 9, 2016).
- NIDA. 2016c. NIH Research on Marijuana and Cannabinoids. <https://www.drugabuse.gov/drugs-abuse/marijuana/nih-research-marijuana-cannabinoids> (accessed December 29, 2016).
- NIDA. 2016d. Marijuana plant material available from the NIDA drug supply program. <https://www.drugabuse.gov/researchers/research-resources/nida-drug-supply-program-dsp/marijuana-plant-material-available-nida-drug-supply-program> (accessed November 3, 2016).
- NIDA. 2016e. Summary of Request for Information (RFI) Regarding Varieties of Marijuana and Marijuana Products for Research. <https://www.drugabuse.gov/drugs-abuse/marijuana/nidas-role-in-providing-marijuana-research/summary-request-information-rfi-regarding-varieties-marijuana-marijuana-products-research> (accessed November 3, 2016).
- NIH (National Institutes of Health). 2016. Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC). https://report.nih.gov/categorical_spending.aspx#legend1 (accessed December 29, 2016).
- NORML (National Organization for the Reform of Marijuana Laws). 2016a. *About Marijuana*. <http://norml.org/marijuana> (accessed December 22, 2016).
- NORML. 2016b. *Election 2016—Marijuana Ballot Results*. <http://norml.org/election-2016> (accessed December 22, 2016).
- Nutt, D. J., L. A. King, and D. E. Nichols. 2013. Effects of Schedule I drug laws on neuroscience research and treatment innovation. *Nature Reviews Neuroscience* 14(8):577–585.
- Pedersen, W. 1990. Reliability of drug use responses in a longitudinal study. *Scandinavian Journal of Psychology* 31(1):28–33.
- Ramaekers, J. G., G. Kauerer, E. L. Theunissen, S. W. Toennes, and M. R. Moeller. 2009. Neurocognitive performance during acute the intoxication in heavy and occasional cannabis users. *Journal of Psychopharmacology* 23(3):266–277.
- Reardon, S. 2015. Marijuana gears up for production high in U.S. labs. *Nature* 519(7543): 269–270.

- Schauer, G. L., B. A. King, R. E. Bunnell, G. Promoff, and T. A. McAfee. 2016. Toking, vaping, and eating for health or fun: Marijuana use patterns in adults, U.S., 2014. *American Journal of Preventative Medicine* 50(1):1–8.
- Schwoppe, D. M., E. L. Karschner, D. A. Gorelick, and M. A. Huestis. 2011. Identification of recent cannabis use: Whole-blood and plasma free and glucuronidated cannabinoid pharmacokinetics following controlled smoked cannabis administration. *Clinical Chemistry* 57(10):1406–1414.
- Stith, S. S., and J. M. Vigil. 2016. Federal barriers to cannabis research. *Science* 352(6290): 1182.
- Taschwer, M., and M. G. Schmid. 2015. Determination of the relative percentage distribution of THCA and $\Delta(9)$ -THC in herbal cannabis seized in Austria—Impact of different storage temperatures on stability. *Forensic Science International* 254:167–171.
- Thomas, B. F., and G. T. Pollard. 2016. Preparation and distribution of cannabis and cannabis-derived dosage formulations for investigational and therapeutic use in the United States. *Frontiers in Pharmacology* 7:285.
- University of Colorado. 2016. *Drug Enforcement Administration (DEA) Controlled Substances*. <http://www.ucdenver.edu/research/EHS/hazmat/Pages/DEA.aspx> (accessed December 22, 2016).
- WDOR (Washington Department of Revenue). 2016a. *Medical Marijuana Taxes*. <http://dor.wa.gov/Docs/Reports/2014/MMJTax.xlsx> (accessed December 8, 2016).
- WDOR. 2016b. *Recreational Marijuana Taxes*. <http://dor.wa.gov/Docs/Reports/2014/RMJTax.xlsx> (accessed December 8, 2016).
- Woodworth, T. W. 2011. How will DEA affect your clinical study? *Journal of Clinical Research Best Practices* 7(12). https://firstclinical.com/journal/2011/1112_DEA.pdf (accessed December 8, 2016).
- Zuurman, L., C. Roy, R. C. Schoemaker, A. Hazekamp, J. den Hartigh, J. C. Bender, R. Verpoorte, J. L. Pinquier, A. F. Cohen, and J. M. van Gerven. 2008. Effect of intrapulmonary tetrahydrocannabinol administration in humans. *Journal of Psychopharmacology* 22(7):707–716.

16

Recommendations to Support and Improve the Cannabis Research Agenda

This is a pivotal time in the world of cannabis policy and research. Shifting public sentiment, conflicting and impeded scientific research, and legislative battles have fueled the debate about what, if any, harms or benefits can be attributed to the use of cannabis or its derivatives. The committee has put forth a substantial number of research conclusions on the health effects of cannabis or cannabinoids. Based on their research conclusions, the members of the committee formulated four specific recommendations to address research gaps, improve research quality, improve surveillance capacity, and address research barriers. The report's full recommendations are described below.

ADDRESS RESEARCH GAPS

To address the research gaps outlined throughout this report, a comprehensive national research agenda will be required. The aspirational goal and organizing principle of this agenda should be to maximize the population-health impact of cannabis research. Achieving this objective will require coordination and collaboration among researchers and research groups; support from stakeholders at the local, state, and national levels; and the concurrent pursuit of several distinct research streams, including clinical and observational research and research in the areas of health policy, health economics, public health, and public safety.

The research agenda should include basic science studies to help inform efforts to minimize harms and maximize benefits associated with

the acute and chronic use of cannabis and cannabinoids, as well as health policy and public health research to examine the health effects of broader social and behavioral changes associated with the legalization of recreational and/or medical cannabis and other changes in cannabis policy. To support the statistical associations identified in epidemiological research, the research agenda should also include basic science research that identifies plausible mechanisms by which cannabis affects specific health endpoints. Furthermore, translational research should be embedded in each of these research streams to ensure that research findings will be of practical use to help inform health care practices, public health priorities, national and state policy, and public safety standards.

Recommendation 1: To develop a comprehensive evidence base on the short- and long-term health effects of cannabis use (both harmful and beneficial effects), public agencies,¹ philanthropic and professional organizations, private companies, and clinical and public health research groups should provide funding and support for a national cannabis research agenda that addresses key gaps in the evidence base. Prioritized research streams and objectives should include, but need not be limited to:

Clinical and Observational Research

- Examine the health effects of cannabis use in at-risk or under-researched populations, such as children and youths (often described as less than 18 years of age) and older populations (generally over 50 years of age), pregnant and breastfeeding women, and heavy cannabis users.
- Investigate the pharmacokinetic and pharmacodynamic properties of cannabis, modes of delivery, different concentrations, in various populations, including the dose–response relationships of cannabis and tetrahydrocannabinol (THC) or other cannabinoids.
- Determine the harms and benefits associated with understudied cannabis products, such as edibles, concentrates, and topicals.
- Conduct well-controlled trials on the potential harmful and beneficial health effects of using different forms of cannabis, such as inhaled (smoked or vaporized) whole cannabis plant and oral cannabis.

¹ Agencies may include the Centers for Disease Control and Prevention (CDC), relevant agencies of the National Institutes of Health (NIH), and the U.S. Food and Drug Administration (FDA).

- Characterize the health effects of cannabis on unstudied and understudied health endpoints, such as epilepsy in pediatric populations; symptoms of posttraumatic stress disorder; childhood and adult cancers; cannabis-related overdoses and poisonings; and other high-priority health endpoints.

Health Policy and Health Economics Research

- Identify models, including existing state cannabis policy models, for sustainable funding of national, state, and local public health surveillance systems.
- Investigate the economic impact of recreational and medical cannabis use on national and state public health and health care systems, health insurance providers, and patients.

Public Health and Public Safety Research

- Identify gaps in the cannabis-related knowledge and skills of health care and public health professionals, and assess the need for, and performance of, continuing education programs that address these gaps.
- Characterize public safety concerns related to recreational cannabis use and evaluate existing quality assurance, safety, and packaging standards for recreational cannabis products.

IMPROVE RESEARCH QUALITY

In order to effectively guide health care decisions and inform public policy, the proposed cannabis research agenda must produce conclusive, actionable evidence. This will require research studies to be carefully designed and rigorously conducted and to have their data results accurately and comprehensively reported.

Ensuring that cannabis research is of uniformly high quality will require the development of guidelines for data collection, standards for research design and reporting, standardized terminology, and a minimum dataset for clinical and epidemiological studies.

Data collection guidelines could prioritize alternate methods for assessing cannabis use, such as whole blood or urine analysis, over those based on self-report or prescriptions. Standards for research design and methodology could require that researchers attempt to account for the confounding effects of alcohol, tobacco, or other relevant substances of abuse. Standards for research reporting could require that authors of systematic reviews report the key demographic characteristics of the study

population, as well as information related to cannabis dose, frequency of use, and route of administration. A universal, standardized terminology would help to create standard units for describing cannabis use. Because much of the existing epidemiological research on cannabis use fails to distinguish between cannabis that is smoked and cannabis that is administered orally, topically, or via other routes, health effects associated with cannabis use may be conflated with those associated with smoking per se. To correct this, future research will need to employ data collection methods that distinguish between different types of cannabis and different routes of cannabis administration.

Wherever possible, these efforts should adapt existing tools to the particular needs and constraints of cannabis research. For example, workshop participants could build on commonly used guidelines and standards for conducting and reporting research, including Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), Consolidated Standards of Reporting Trials (CONSORT), Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), and Cochrane guidelines for systematic reviews.

Adequately addressing these topics will require input from numerous stakeholders, including clinical and public health cannabis researchers; research methodologists; representatives from working groups that have developed research reporting guidelines; organizations engaged in standards development; representatives from scientific publications; and representatives from government agencies directly or indirectly involved in the research process, including the U.S. Department of Health and Human Services (HHS), including CDC and NIH, and FDA.

Recommendation 2: To promote the development of conclusive evidence on the short- and long-term health effects of cannabis use (both harmful and beneficial effects), agencies of the U.S. Department of Health and Human Services, including the National Institutes of Health and the Centers for Disease Control and Prevention, should jointly fund a workshop to develop a set of research standards and benchmarks to guide and ensure the production of high-quality cannabis research. Workshop objectives should include, but need not be limited to:

- The development of a minimum dataset for observational and clinical studies, standards for research methods and design, and guidelines for data collection methods.
- Adaptation of existing research-reporting standards to the needs of cannabis research.

- The development of uniform terminology for clinical and epidemiological cannabis research.
- The development of standardized and evidence-based question banks for clinical research and public health surveillance tools.

IMPROVE SURVEILLANCE CAPACITY

The development of a comprehensive and conclusive evidence base on the health effects of cannabis must begin with data collection. In turn, data collection on a scale sufficient to guide state and national policy will require a diverse array of powerful surveillance tools and technologies.

In many cases, existing surveillance tools can be adapted to further the cannabis research agenda. For example, a recurrent and comprehensive set of cannabis-related questions could be added to existing national health surveys. Researchers could use the Behavioral Risk Factor Surveillance System to track changes in the prevalence of medical and recreational cannabis use; the Medical Expenditure Panel Survey to assess the impact of medical cannabis laws on health care treatments and costs; and the National Vital Statistics System to monitor changes in the incidence rate of cannabis-related overdose deaths.

In other cases, novel diagnostic technologies will need to be developed to aid data collection efforts. For example, the growing incidence of cannabis poisonings among children and the demonstrated risks associated with driving under the influence of cannabis underscore the need for rapid and noninvasive methods of assessing for acute cannabis intoxication.

Multiple stakeholders can contribute to these efforts. CDC's Center for Surveillance, Epidemiology and Laboratory Services, the Questionnaire Design Research Laboratory at the National Center for Health Statistics, and the Center for Behavioral Health Statistics and Quality at the Substance Abuse and Mental Health Services Administration (SAMHSA) can aid in the design and evaluation of survey questions that accurately capture key data points relating to cannabis use. State public health departments can collaborate with Association of Public Health Laboratories to use existing public health laboratories to provide diagnostic tools and other laboratory resources to meet the needs of clinical and public health professionals engaged in cannabis research. Because of differences in cannabis product type, availability, access, and regulation, such surveillance efforts need to be state based, for the time being.

In their potential role as conveners, the National Association of County and City Health Officials (NACCHO) and the Association of State and Territorial Health Officials (ASTHO) can aid federal agencies

and state and local health departments in assessing the capacity to expand the resources of public health surveillance systems, as well as in articulating strategies and prioritizing the actions necessary to meet the needs of a comprehensive cannabis research agenda.

Recommendation 3: To ensure that sufficient data are available to inform research on the short- and long-term health effects of cannabis use (both harmful and beneficial effects), the Centers for Disease Control and Prevention, the Substance Abuse and Mental Health Services Administration, the Association of State and Territorial Health Officials, the National Association of County and City Health Officials, the Association of Public Health Laboratories, and state and local public health departments should fund and support improvements to federal public health surveillance systems and state-based public health surveillance efforts. Potential efforts should include, but need not be limited to:

- The development of question banks on the harmful and beneficial health effects of therapeutic and recreational cannabis use and their incorporation into major public health surveys, including the National Health and Nutrition Examination Survey, National Health Interview Survey, Behavioral Risk Factor Surveillance System, National Survey on Drug Use and Health, Youth Risk Behavior Surveillance System, National Vital Statistics System, Medical Expenditure Panel Survey, and National Survey of Family Growth.
- Determining the capacity to collect and reliably interpret data from diagnostic classification codes in administrative data (e.g., *International Classification of Diseases-10*).
- The establishment and utilization of state-based testing facilities to analyze the chemical composition of cannabis and products containing cannabis, cannabinoids, or THC.
- The development of novel diagnostic technologies that allow for rapid, accurate, and noninvasive assessment of cannabis exposure and impairment.
- Strategies for surveillance of harmful effects of cannabis for therapeutic use.

ADDRESS RESEARCH BARRIERS

The designation of cannabis as a Schedule I substance imposes numerous regulatory barriers that limit access to the funding and material

resources necessary to conduct cannabis research. Unless these barriers are directly addressed, or creative solutions are developed to circumvent the challenges they pose, a comprehensive national cannabis research agenda will remain an elusive goal.

The evidence discussed in this report suggests that cannabis has both therapeutic value and public health risks. The public health case for pursuing cannabis research, which is premised on this potential for both harm and benefit, is sharpened by the increased prevalence of cannabis use in states where medical and recreational cannabis has been legalized.

To ensure that policy makers are better informed to make decisions on cannabis research and policy, and to explore and characterize the full scope of political and nonpolitical strategies for resolving regulatory barriers to cannabis research, an objective and evidence-based analysis of cannabis policy is necessary.

Recommendation 4: The Centers for Disease Control and Prevention, National Institutes of Health, U.S. Food and Drug Administration, industry groups, and nongovernmental organizations should fund the convening of a committee of experts tasked to produce an objective and evidence-based report that fully characterizes the impacts of regulatory barriers to cannabis research and that proposes strategies for supporting development of the resources and infrastructure necessary to conduct a comprehensive cannabis research agenda. Committee objectives should include, but need not be limited to:

- Proposing strategies for expanding access to research-grade marijuana, through the creation and approval of new facilities for growing and storing cannabis.
- Identifying nontraditional funding sources and mechanisms to support a comprehensive national cannabis research agenda.
- Investigating strategies for improving the quality, diversity, and external validity of research-grade cannabis products.

Appendix A

Glossary

Δ^9 -tetrahydrocannabinol (THC)—the main psychoactive constituent of cannabis.

adjusted odds ratio (aOR)—an odds ratio that controls for confounding variables.

Ashworth scale—a clinical measure of muscle spasticity based on an assessment of a patient’s muscle tone in different muscle groups.

association—the statistical relation between two or more events, characteristics, or other variables.

cannabidiol (CBD)—a constituent of cannabis that has been traditionally considered non-psychoactive.

cannabinoid—one of a class of chemical compounds that act on cannabinoid receptors, cannabinoids can be naturally derived from the cannabis plant or manufactured.

cannabis—a broad term that can be used to describe the various products and chemical compounds derived from the *Cannabis sativa* or *Cannabis indica* species.

cannabis use disorder (CUD)—according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, a problem-causing pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least two distinguishing symptoms (e.g., cannabis is taken in larger amounts or for longer periods than intended; experience of craving; continued cannabis use despite the experience of physical, social, or interpersonal problems caused by cannabis use) occurring within a 12-month period.

case series—an analysis of a series of people with the disease (there is no comparison group in case series). Case series studies provide weaker evidence than case-control studies.

case-control study—an observational analytic study that enrolls one group of persons with a certain disease, chronic condition, or type of injury (case-patients) and a group of persons without the health problem (control subjects) and compares differences in exposures, behaviors, and other characteristics to identify and quantify associations, test hypotheses, and identify causes.

cohort study—an observational analytic study in which enrollment is based on one's status of exposure to a certain factor or membership in a certain group. Populations are followed, and disease, death, or other health-related outcomes are documented and compared. Cohort studies can be either prospective or retrospective.

comparator—the agent to which the experimental arm of a study is compared (e.g., placebo, usual care, active control).

control—comparator against which the study treatment is evaluated (e.g., concurrent [placebo, no treatment, dose-response, active], and external [historical, published literature]).

cross-sectional study—a study in which a sample of persons from a population are enrolled and their exposures and health outcomes are measured simultaneously; a survey.

cultivar—a plant variety that has been produced in cultivation by selective breeding.

dose—the quantity of a drug that is used at one time or in fractional amounts during a given period of time.

dronabinol—a synthetic cannabinoid for oral administration, similar to tetrahydrocannabinol (THC). It is the active ingredient in Marinol®.

evidence—information on which a conclusion about a cause-effect relationship is based. The most direct evidence for health effects in humans is usually based on studies of health endpoints that are conducted in humans, including randomized trials and nonrandomized epidemiologic studies. Additional evidence can be provided by studies of intermediate endpoints or markers in humans as well as by nonhuman studies. The committee has developed a strength-of-evidence table so that the level of evidence is expressed in uniform terms and calibrated throughout the report (see Appendix B).

exclusion criteria—a list of characteristics in a protocol, any one of which may exclude a potential subject from participation in a study.

hazard ratio (HR)—the weighted relative risk of an outcome (e.g., death) during the entire study period; often reported in the context of survival analysis.

health effects—the positive and negative health outcomes resulting from exposure to cannabis or cannabis-derived products.

incidence—the number of new cases of a condition, symptom, death, or injury that develop during a specified period of time.

inclusion criteria—the criteria in a protocol that prospective subjects must meet to be eligible for participation in a study.

marijuana—a *Cannabis sativa* plant-derived product typically composed from the plant's dried leaves, stems, seeds, and buds.

meta-analysis—a statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a more precise summary estimate of the effect on a particular outcome. Meta-analyses are frequently used in systematic reviews.

morbidity—any departure, subjective or objective, from a state of physiological or psychological health and well-being (e.g., disease, injury, disability).

mortality—death or loss of life.

nabilone—a synthetic cannabinoid for oral administration, similar to tetrahydrocannabinol (THC). It is the active ingredient in Cesemet[®].

narrative review—narrative reviews tend to be mainly descriptive, do not involve a systematic search of the literature, and thereby often focus on a subset of studies in an area chosen based on availability or author selection. Generally, narrative reviews offer lower-quality evidence than systematic reviews. For this reason, and for the purpose of the report, narrative reviews are classified as primary literature.

observational study—a study in which the investigator observes rather than influences exposure and disease among participants. Case-control and cohort studies are examples of observational studies.

odds ratio (OR)—one measure of treatment effectiveness. It is the odds of an event happening in the experimental group expressed as a proportion of the odds of an event happening in the control group. The closer the OR is to 1, the smaller the difference in effect is between the experimental intervention and the control intervention. If the OR is greater (or less) than 1, then the effects of the treatment are more (or less) than those of the control treatment. Note that the effects being measured may be adverse (e.g., death or disability) or desirable (e.g., survival). When events are rare, the OR is analogous to the relative risk (RR), but as event rates increase, the OR and RR diverge.

outcome—events or experiences that clinicians or investigators examining the impact of an intervention or exposure measure because they believe such events or experiences may be influenced by the intervention or exposure.

pooled estimate—an average derived from multiple studies with varying data but with a common measurement. Typically found in systematic reviews and meta-analyses.

potency—the amount of drug required to produce a specific level of effect.

preclinical—research studies that use cell culture or animal models to test scientific hypotheses. These studies are performed prior to clinical studies that use human subjects.

prevalence—the number or proportion of individuals within a given population who share a specific characteristic.

primary literature—peer-reviewed accounts of original research that contribute new evidence to science. By comparison, systematic reviews and literature reviews analyze existing evidence. Examples of the types of primary literature used in the report are randomized controlled trials, cohort studies, cross-sectional studies, case-control studies, and case series.

problem cannabis use—a symptom of cannabis use disorder. Problem cannabis use includes the experience of persistent or recurrent social, interpersonal, occupational, academic, recreational, psychological, or physical problems caused or exacerbated by cannabis use.

randomized controlled trial (RCT)—a trial in which participants are randomly assigned to one of two or more groups, at least one of which (the experimental group) receives an intervention that is being tested and another (the comparison or control group) receives an alternative treatment or placebo. This design allows assessment of the relative effects of interventions.

relative risk (RR)—a ratio of the risk of an event among an exposed population to the risk among the unexposed.

route of administration—the path by which a drug is taken into the body.

systematic review—research that summarizes the evidence on a clearly formulated question according to a predefined protocol. Systematic and explicit methods to identify, select, and appraise relevant studies and to extract, collate, and report their findings are used. Statistical meta-analysis may or may not be used. Systematic reviews were the optimal data source for identifying associations between cannabis exposure and all of the health endpoints discussed in this report.

Appendix B

Study Approach

In response to its charge, the committee developed a process defined by discrete actions building toward an evidence base that would eventually inform the committee's findings and conclusions. This process is depicted in Figure B-1.

The following sections detail the process by which the committee came to their conclusions about the weight of evidence regarding the association between cannabis and specific health endpoints. The steps include the literature search, the refinement of the specific health endpoints of medical and public health importance to be assessed, the identification and assessment of relevant literature (including published systematic reviews and primary literature), and the development of consistent and specific language to describe the integration of the literature to reflect the weight of evidence.

LITERATURE SEARCH

A professional research librarian worked with the committee to conduct the literature searches used to identify relevant research. Six searches were conducted. An initial search (Search 1) of Medline, Embase, and the Cochrane Database of Systematic Reviews found 19,189 total articles reporting on associations between cannabis exposure and health endpoints. Search 1 included articles that were published between January 1999 and June 2016 and that included a cannabis search term and search terms relevant to health effects of interest in at least one of several search



FIGURE B-1 Summary of the committee’s process.

fields (e.g., title, abstract, subject heading). A partial review of the search results found a large number of irrelevant documents. For this reason, a second and more limited search strategy was developed.

Search 2 involved the same databases as Search 1 but used different search terms to identify articles associated with specific health endpoints, and it excluded articles with specific terms (e.g., “animal,” “spice”) in the title or abstract. Search 2 produced 2,092 articles between 1999 and the 2016. The substantial reduction in articles indicated that the more limited search strategy caused relevant research to be excluded; consequently, a third and broader search strategy was developed.

Search 3 of the same databases produced 7,198 total articles reporting on associations between cannabis exposure and any health endpoint. This search included articles published between 1999 and 2016, excluded articles with specific terms (e.g., “mice,” “spice”) in the title or abstract, and limited articles by study design (e.g., clinical trial, observational study, systematic review).

The results of Search 2 and Search 3 were combined, and three additional searches were conducted in order to address potential gaps in the overall search results. Search 4 identified 1,396 articles in the PsycINFO database, filling gaps in the committee’s collection of literature on the effects of cannabis exposure on mental health and psychosocial endpoints. Using the search term “Nabilone” (a synthetic cannabinoid), Search 5 identified 33 articles in Medline, Embase, and the Cochrane Database of Systematic Reviews that previous searches had not included. Search 6 identified 389 articles and brought the literature up to date by extending the date of publication parameter to August 2, 2016, and including articles published electronically ahead of print. The terms and strategies used in these searches are provided on page 419 of this appendix. In addition to these six searches, committee members also reviewed their personal libraries, and added potentially relevant articles from these collections to the combined search results.

The results from searches 2 through 6 were combined to create a master library containing 10,759 unique articles, including 1,488 articles initially categorized as systematic reviews. These articles were then sorted into seven major health endpoint topic areas: injury and mortality; car-

diovascular and respiratory symptoms and conditions; cancer, immune function, and infections; mental health symptoms and conditions; prenatal, perinatal, and postnatal health effects; psychosocial health effects; and therapeutic health effects.¹ Upon further reflection and review of the available literature, the committee decided to separate the original cardiovascular and respiratory topic area into two individual research topics, as well as to separate out two additional research topics—problem cannabis use, and cannabis use and abuse of other substances—from the original mental health topic area. This final list of topic areas was subsequently divided into the 11 health endpoint topic areas covered in the chapters that comprise parts II and III of the report. Within each of these topic areas the committee identified specific research questions relating to health endpoints of medical and public health importance that would be the focus of the report. They based this list on their public health and medical expertise, their knowledge of the cannabis literature, input from the sponsors at the first meeting, and other key reviews about the health effects of cannabis. This process, which reduced the total number of articles to be reviewed by the committee, was necessary to make the scope of the report manageable, but it may have resulted in the exclusion of certain health outcomes of interest to health professionals, researchers, policy makers, or the public. Below, Box B-1 lists the health topic areas and specific health endpoints selected for review by the committee.

After filtering the original search results for articles relevant to the health endpoints of interest, 6,540 primary literature articles and 288 systematic reviews were left to be reviewed by the committee. Given the large number of potentially relevant articles, the committee decided to begin by reviewing the identified systematic reviews. To accomplish this, the committee modified previously developed approaches for evaluating the quality of the systematic reviews and primary literature. These approaches are described in the systematic review: identification and quality review, “Primary Literature: Identification and Quality Review,” and “Data Synthesis and Strength of Evidence Assessment” sections below.

The committee identified articles as possibly being systematic reviews based on abstracts or keyword searches, and then they evaluated each of the identified articles for the presence of the key elements of a systematic review by asking the following questions:

¹ The organization of Search 2 results involved different search terms and tools than the organization of Search 3 results. Search 2 topic groups were developed using unique search terms, online databases (Medline, Embase, Cochrane Database of Systematic Reviews), and Ovid search functions. Search 3 topics groups were developed using unique search terms, the Search 3 EndNote library, and the EndNote full-text keyword search function.

BOX B-1
Health Topics and Prioritized Health Endpoints
(listed in the order in which they appear in the report)

Therapeutic effects

- Chronic pain; cancer, chemotherapy-induced nausea/vomiting; anorexia and weight loss; irritable bowel syndrome; epilepsy; spasticity related to multiple sclerosis or spinal cord injury; Tourette syndrome; amyotrophic lateral sclerosis; Huntington's disease; Parkinson's disease; dystonia; dementia; glaucoma; traumatic brain injury; addiction; anxiety; depression; sleep disorders; posttraumatic stress disorder; schizophrenia and other psychoses

Cancer

- Lung cancer; head and neck cancer; testicular cancer; esophageal cancer; other cancer

Cardiometabolic risk

- Acute myocardial infarction; stroke; metabolic dysregulation, metabolic syndrome, prediabetes, and diabetes mellitus

Respiratory disease

- Pulmonary function; chronic obstructive pulmonary disorder; respiratory symptoms (including chronic bronchitis); asthma

Immunity

- Immune function; infectious disease

1. Does the article describe a search involving at least two databases?
2. Does the article describe a search involving appropriate search terms?
3. Does the article describe a search involving prespecified eligibility criteria?
4. Does the article include a risk-of-bias discussion and/or quality assessment?
5. Does the article include a meta-analysis or qualitative synthesis of findings?
6. Does the article report on one or more health effects of cannabis on humans?

Injury and death

- All-cause mortality; occupational injury; motor vehicle crash; overdose injury and death

Prenatal, perinatal, and postnatal exposure to cannabis

- Pregnancy complications for the mother; fetal growth and development; neonatal conditions; later outcomes for the infant

Psychosocial

- Cognition (learning, memory, attention, intelligence); academic achievement and educational outcomes; employment and income; social relationships and other social roles

Mental health

- Schizophrenia and other psychoses; bipolar disorders, depression; suicide; anxiety; posttraumatic stress disorder

Problem cannabis use

- Cannabis use disorder

Cannabis use and abuse of other substances

- Abuse of other substances

Articles that were deemed true systematic reviews using the above questions as a guideline were then assessed for quality based on five attributes adapted from other sources (Higgins et al., 2011). In their assessment of the quality of a systematic review, committee members considered the study eligibility criteria, how studies were identified and considered for inclusion, how data were collected and appraised by the authors, the methods by which study findings were selected and synthesized, and whether any conflict of interests were addressed. Box B-2 lists the specific questions committee members were asked to consider in the quality assessment.

Based on the responses to these questions, the overall quality of the systematic review was rated as good, fair, or poor. To ensure the accuracy

BOX B-2
Quality Assessment Questions

QUESTION

*Rate your level of concern (high or low) regarding study eligibility criteria.
Your response should be informed by the following questions:*

Study eligibility criteria

- Was an “a priori” design provided?
- Were study eligibility criteria clearly specified?
- Were restrictions in eligibility criteria appropriate?

Identification and collection of studies

- Was a comprehensive literature search performed?
- Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?
- Were restrictions based on date, publication format, or language appropriate?
- Was selection bias avoided?

Data collection and study appraisal

- Were at least two individuals involved in study selection and data extraction?
- Were the characteristics of the included studies provided?
- Was the scientific quality of the included studies assessed and documented?

Synthesis and findings

- Was the scientific quality of the included studies used appropriately in formulating conclusions?
- Were the methods used to combine the findings of studies appropriate?
- Was between-study variation (heterogeneity) minimal or addressed in the synthesis?
- Was the likelihood of publication bias assessed?
- Are the stated conclusions supported by the data presented?

Conflict of interest

- Was the conflict of interest for the systematic review stated?

Overall quality

- Rate the overall quality of the systematic review

of quality assessments, all systematic reviews were rated independently by at least two committee members. Disagreements among committee members regarding the overall quality of a systematic review were resolved through deliberation or by the assessment of a third committee member. Only those systematic reviews rated as good or fair quality were used to inform the report's findings, conclusions, and recommendations.

PRIMARY LITERATURE: IDENTIFICATION AND QUALITY REVIEW

For those health endpoints addressed by more than one good- or fair-quality systematic review, the committee gave primacy to the most recently published systematic reviews (since 2011). Any deviations in this process are detailed in the chapter text. For every health endpoint with an associated good- or fair-quality systematic review, the committee also reviewed relevant primary literature published after the cutoff date of the literature search used in that systematic review. For endpoints not addressed by at least one good- or fair-quality systematic review, the committee reviewed all relevant primary literature published between January 1, 1999, and August 2, 2016.

Committee members first reviewed article abstracts to identify and remove editorials, opinion pieces, grey literature, and other documents that were not peer-reviewed cross-sectional studies, case-control studies, cohort studies, randomized controlled trials (RCTs), or nonsystematic literature reviews. During this preliminary review, committee members also assessed the relevance of the article to the health endpoint question.

In their in-depth review of the primary literature, committee members were guided by the Cochrane Quality Assessment for randomized controlled trials and the Newcastle–Ottawa Scale for cohort and case-control studies.² For a depiction of the flow of articles through the search and selection process, see Figure B-2.

DATA SYNTHESIS AND STRENGTH OF EVIDENCE ASSESSMENT

After completing the identification and quality-assessment process described above, the committee formulated its findings and conclusions.

² The Cochrane Risk Assessment Tool was designed to assess for a risk of bias consequent to flaws in the design, conduct, analysis, and reporting of randomized trials (Higgins, 2011). The Newcastle–Ottawa Scale (NOS) was designed to assess the quality of nonrandomized trials to be included in a systematic review. The NOS assesses studies along three dimensions: selection of study groups, comparability of study groups, and determination of endpoints and exposures (Wells et al., 2011).

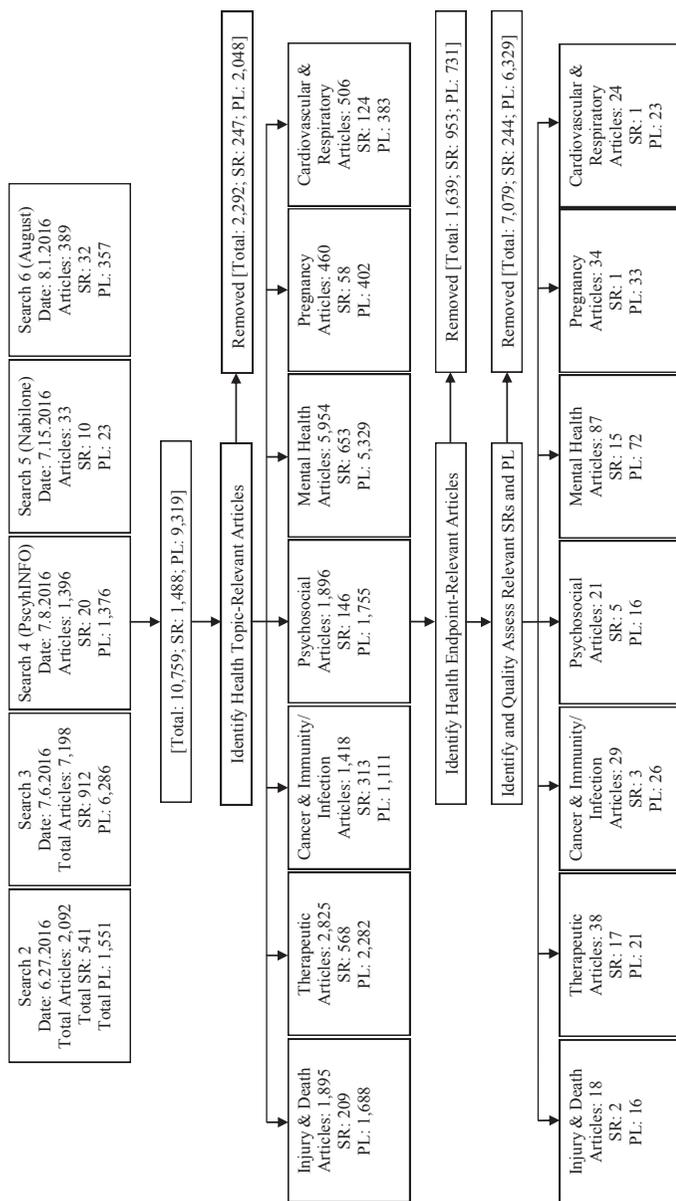


FIGURE B-2 Search and selection process flow chart.
 NOTE: Totals within and across searches and health topic areas may not sum due to duplication of articles and hand-searching efforts.

The committee employed two strategies to ensure that report conclusions and recommendations were based on the best available evidence and that the strength of the evidence informing the conclusions was explicitly articulated. First, the committee privileged evidence drawn from RCTs, followed by nonrandomized controlled trials, prospective controlled studies, and case-control studies. Case series and case studies were referenced only in the absence of higher-quality studies. Second, the committee developed a set of standardized terms to describe the strength of the evidence informing every conclusion. Informed by the reports of previous Institute of Medicine (IOM)³ committees, the committee developed standard language to categorize the weight of evidence regarding whether cannabis or cannabinoid use (for therapeutic purposes) is an effective or ineffective treatment for the prioritized health endpoints of interest, or whether cannabis or cannabinoid use (primarily for recreational purposes) is statistically associated with the prioritized health endpoints of interest. The weight of the evidence was determined during private deliberations of subgroups of the committee. This hierarchy of evidence does not imply the magnitude of the observed effect or the importance of the health effect from an individual or population standpoint. Instead, these terms reflect the quality, quantity, and consistency of the evidence supporting a conclusion. See Box B-3 for the terms and their descriptions.

DISCUSSION

The search strategies and processes described above were developed and adopted by the committee in order to adequately address a broad statement of task in a limited time frame, while adhering to the National Academies of Sciences, Engineering, and Medicine's high standards for the quality and rigor of committee reports. Some limitations to these strategies and processes are discussed below.

First, the committee was not tasked to conduct a systematic review, which would have required a lengthy and robust series of processes. The committee did, however, adopt key features of that process: a comprehensive literature search, assessments by more than one person of the quality (risk of bias) of key literature and the conclusions, prespecification of the questions of interest before conclusions were formulated, standard language to allow comparisons between conclusions, and declarations of conflict of interest via the National Academies conflict of interest policies. Second, there is a possibility that some literature was missed because of the practical steps taken to narrow a very large literature to one that was

³ As of March 2016, the Health and Medicine Division continues the consensus studies and convening activities previously carried out by the Institute of Medicine (IOM).

BOX B-3
Weight-of-Evidence Categories**CONCLUSIVE EVIDENCE**

For therapeutic effects: There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence from randomized controlled trials to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are many supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

SUBSTANTIAL EVIDENCE

For therapeutic effects: There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good-quality studies with very few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

MODERATE EVIDENCE

For therapeutic effects: There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

manageable within the time frame available to the committee. Furthermore, very good research may not be reflected in this report because it did not directly address the health endpoint questions that the committee formulated.

For other health effects: There is some evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good- to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

LIMITED EVIDENCE

For therapeutic effects: There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is weak evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

NO OR INSUFFICIENT EVIDENCE TO SUPPORT THE ASSOCIATION

For therapeutic effects: There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is no or insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors.

SEARCH STRATEGIES

Search 2

Date: June 27, 2016

Total citations:

Systematic reviews: 541

Primary literature: 1,551

Total: 2,092

Databases (search engine): Medline (Ovid); Embase (Ovid); Cochrane (Ovid)

Note: Ovid command-line syntax is provided below. Terms immediately followed by a forward slash (/) are Medical Subject Headings (MESH headings from MEDLINE) or EMTREE terms (from the EMBASE controlled vocabulary). The fields searched by a .mp in Embase and Medline include title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, and unique identifier. The fields searched by a .mp in Cochrane include title, short title, abstract, full text, keywords, caption text.

Search No.	Search Syntax
Beneficial	
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	spice.ti,ab.
12	K2.ti,ab.
13	or/11–12
14	10 not 13
15	Rats/ or rats.ti,ab.
16	Mice/ or mice.ti,ab.
17	animals/ or animals.ti,ab.
18	or/15–17
19	14 not 18
20	Therapeutics/
21	“therapeutic use”.mp.
22	benefits.mp.
23	treatment.mp.
24	therapy.mp.
25	Palliative Care/ or palliation.mp.
26	“Quality of Life”/
27	or/20–26

Search No.	Search Syntax
28	19 and 27
29	Nausea/ or nausea.mp.
30	Vomiting/
31	vomiting.mp.
32	or/28–30
33	28 and 31
34	limit 32 to (abstracts and English language and humans and yr="1999–Current")
35	Analgesia/ or Analgesia.mp.
36	28 and 35
37	limit 36 to (English language and humans and yr="1999–Current")
38	Anxiety/ or anxiety relief.mp. or Anxiety Disorders/
39	28 and 38
40	limit 39 to (English language and humans and yr="1999–Current")
41	irritable bowel syndrome.mp. or Irritable Bowel Syndrome/
42	28 and 41
43	limit 42 to (English language and humans and yr="1999–Current")
44	improved sexual function.mp. or Sexual Behavior/
45	sexual function.mp.
46	or/44–45
47	28 and 46
48	limit 47 to (English language and humans and yr="1999–Current")
49	Interpersonal Relations/ or social relationships.mp.
50	28 and 57
51	limit 50 to (English language and humans and yr="1999–Current")
52	increased appetite.mp. or Appetite/ or Eating/
53	wasting.mp. or Wasting Syndrome/
54	or/52–53
	28 and 54
55	limit 54 to (English language and humans and yr="1999–Current")
56	Substance-Related Disorders/ or addiction.mp.
57	28 and 56
58	limit 57 to (English language and humans and yr="1999–Current")
59	intraocular pressure.mp. or Intraocular Pressure/
60	28 and 59
61	limit 60 to (English language and humans and yr="1999–Current")
62	PTSD.mp. or Stress Disorders, posttraumatic/
63	trauma.mp.
64	or/62–63
65	28 and 64
66	limit 65 to (English language and humans and yr="1999–Current")

Search No.	Search Syntax
67	Premenstrual Syndrome/ or Premenstrual Dysphoric Disorder/ or premenstrual.mp.
68	28 and 67
69	limit 68 to (English language and humans and yr="1999-Current")
70	Epilepsy/ or seizure control.mp. or Seizures/
71	28 and 70
72	limit 71 to (English language and humans and yr="1999-Current")
73	sleep disorders.mp. or Sleep Wake Disorders/
74	insomnia.mp. or "Sleep Initiation and Maintenance Disorders"/
75	or/73-74
76	28 and 75
77	limit 76 to (English language and humans and yr="1999-Current")
78	Muscle Spasticity/ or Spasticity.mp.
79	Pain/
80	Multiple Sclerosis/
81	or/78-80
82	28 and 81
83	limit 82 to (English language and humans and yr="1999-Current")
84	cancer treatment.mp.
85	cancer prevention.mp.
86	or/84-85
87	28 and 86
88	limit 87 to (English language and humans and yr="1999-Current")
89	brain injury.mp. or Brain Injuries/
90	28 and 89
91	limit 90 to (English language and humans and yr="1999-Current")
92	34 or 37 or 40 or 43 or 48 or 51 or 55 or 58 or 61 or 66 or 69 or 72 or 77 or 83 or 88 or 91
93	limit 92 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
94	34 or 37 or 40 or 43 or 48 or 51 or 55 or 58 or 61 or 66 or 69 or 72 or 77 or 83 or 88 or 91
95	limit 94 to (meta-analysis or systematic reviews)

Search No.	Search Syntax
Cancer	
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/

Search No.	Search Syntax
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	spice.ti,ab.
12	K2.ti,ab.
13	or/11–12
14	Rats/ or rats.ti,ab.
15	Mice/ or mice.ti,ab.
16	animals/ or animals.ti,ab.
17	or/14–16
18	10 not 13
19	cancer.mp. or Neoplasms/
20	lung cancer.mp. or Lung Neoplasms/
21	Esophageal Neoplasms/ or Pharyngeal Neoplasms/ or Laryngeal Neoplasms/ or “Head and Neck Neoplasms”/ or upper aerodigestive tract cancer.mp. or Mouth Neoplasms/
22	testicular cancer.mp. or Testicular Neoplasms/
23	childhood cancer.mp.
24	immune system.mp. or Immune System/
25	Immunity/
26	immunity.mp.
27	or/19–26
28	18 and 27
29	28 not 17
30	limit 29 to (human and English language and yr=“1999–Current”)
31	limit 30 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
32	limit 30 to (meta analysis or systematic reviews)
Search No.	Search Syntax
Cardiovascular	
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/

Search No.	Search Syntax
8	THC.mp.
9	marinol.mp.
10	or/1-9
11	Cardiovascular Abnormalities/ or Cardiovascular Diseases/ or cardiovascular.mp.
12	cerebrovascular.mp. or Cerebrovascular Disorders/
13	Peripheral Vascular Diseases/ or peripheral vascular.mp.
14	heart attack.mp. or Myocardial Infarction/
15	Stroke/ or stroke risk.mp.
16	thromboangiitis obliterans.mp. or Thromboangiitis Obliterans/
17	spice.ti,ab.
18	K2.ti,ab.
19	or/17-18
20	10 not 19
21	Rats/ or rats.ti,ab.
22	Mice/ or mice.ti,ab.
23	animals/ or animals.ti,ab.
24	or/21-23
25	or/11-16
26	20 and 25
27	26 not 24
28	27
29	limit 28 to (English language and humans and yr="1999-Current")
30	limit 29 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
31	limit 29 to (meta analysis or systematic reviews)

Search No.	Search Syntax
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Injury

1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1-9
11	spice.ti,ab.

Search No.	Search Syntax
12	K2.ti,ab.
13	or/11–12
14	Rats/ or rats.ti,ab.
15	Mice/ or mice.ti,ab.
16	animals/ or animals.ti,ab.
17	or/14–16
18	injury.mp. or “Wounds and Injuries”/
19	10 and 18
20	19 not 13
21	20 not 17
22	21
23	limit 22 to (English language and humans and yr=“1999–Current”)
24	Accidents, Traffic/ or motor vehicle accident.mp.
25	motor vehicle crash.mp.
26	or/24–25
27	10 and 26
28	27 not 13
29	28 not 17
30	29
31	limit 30 to (English language and humans and yr=“1999–Current”)
32	all-cause death.mp.
33	Death/
34	or/32–33
35	10 and 34
36	35 not 13
37	36 not 17
38	37
39	limit 38 to (English language and humans and yr=“1999–Current”)
40	Drug Overdose/
41	overdose death.mp.
42	or/40–41
43	10 and 42
44	43 not 13
45	44 not 17
46	45
47	limit 46 to (English language and humans and yr=“1999–Current”)
48	limit 23 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)

Search No.	Search Syntax
49	limit 31 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
50	limit 39 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
51	limit 47 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
52	limit 23 to (meta analysis or systematic reviews)
53	limit 31 to (meta analysis or systematic reviews)
54	limit 39 to (meta analysis or systematic reviews)
55	limit 47 to (meta analysis or systematic reviews)

Search No.	Search Syntax
Mental Health	
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	spice.ti,ab.
12	K2.ti,ab.
13	or/11–12
14	Rats/ or rats.ti,ab.
15	Mice/ or mice.ti,ab.
16	animals/ or animals.ti,ab.
17	or/14–16
18	10 not 13
19	mental disease/ or mental health/
20	18 and 19
21	20 not 17
22	21
23	limit 22 to (human and English language and yr="1999–Current")

Search No.	Search Syntax
24	limit 23 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
25	limit 24 to (journal and article)
26	limit 24 to (meta analysis or "systematic review")
27	limit 26 to (journal and (article or review))
28	cannabis addiction/
29	drug abuse/ or drug misuse/
30	cannabis dependence.mp.
31	or/28–30
32	18 and 31
33	32 not 17
34	33
35	limit 34 to (human and english language and yr="1999–Current")
36	limit 35 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
37	limit 36 to (journal and article)
38	limit 35 to (meta analysis or "systematic review")
39	limit 38 to (journal and (article or review))
40	alcohol abuse/
41	tobacco dependence/ or tobacco consumption/
42	"tobacco use"/
43	drug abuse/
44	drug dependence/
45	or/40–44
46	18 and 45
47	46 not 17
48	47
49	limit 48 to (human and English language and yr="1999–Current")
50	limit 49 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
51	limit 50 to (journal and article)
52	limit 49 to (meta analysis or "systematic review")
53	limit 52 to (journal and (article or review))
54	schizophrenia/
55	psychosis/
56	psychotic disorder.mp.
57	or/54–56
58	18 and 57
59	58 not 17

Search No.	Search Syntax
60	59
61	limit 60 to (human and English language and yr="1999–Current")
62	limit 61 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
63	limit 62 to (journal and article)
64	limit 61 to (meta analysis or "systematic review")
65	limit 64 to (journal and (article or review))
66	depression/
67	18 and 66
68	67 not 17
69	68
70	limit 69 to (human and English language and yr="1999–Current")
71	limit 70 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
72	limit 71 to (journal and article)
73	limit 70 to (meta analysis or "systematic review")
74	limit 73 to (journal and (article or review))
75	suicide/
76	18 and 75
77	76 not 17
78	77
79	limit 78 to (human and English language and yr="1999–Current")
80	limit 78 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
81	limit 80 to (journal and article)
82	limit 79 to (meta analysis or "systematic review")
83	limit 82 to (journal and (article or review))
84	anxiety/
85	18 and 84
86	85 not 17
87	86
88	limit 87 to (human and English language and yr="1999–Current")
89	limit 88 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)
90	limit 89 to (journal and article)
91	limit 88 to (meta analysis or "systematic review")
92	limit 91 to (journal and (article or review))

Search No.	Search Syntax
	Pregnancy
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	spice.ti,ab.
12	K2.ti,ab.
13	or/11–12
14	Rats/ or rats.ti,ab.
15	Mice/ or mice.ti,ab.
16	animals/ or animals.ti,ab.
17	or/14–16
18	10 not 13
19	pregnancy outcomes.mp. or pregnancy outcome/
20	low birthweight.mp. or low birth weight/
21	premature labor/ or pre term delivery.mp.
22	birth defects.mp.
23	stillbirth/
24	miscarriage.mp. or spontaneous abortion/
25	neonatal mortality.mp. or newborn mortality/
26	physical growth.mp. or growth/
27	18 and 19
28	27 not 17
29	28
30	limit 29 to (human and english language)
31	18 and 20
32	31 not 17
33	32
34	limit 33 to (human and English language and yr="1999–Current")
35	18 and 21
36	35 not 17
37	36
38	limit 37 to (human and English language and yr="1999–Current")
39	18 and 22
40	39 not 17

Search No.	Search Syntax
41	40
42	limit 41 to (human and English language and yr="1999-Current")
43	or/23-25
44	18 and 43
45	18 and 43
46	45 not 17
47	46
48	46
49	limit 48 to (human and English language and yr="1999-Current")
50	18 and 26
51	50 not 17
52	51
53	limit 52 to (human and English language and yr="1999-Current")
54	limit 30 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
55	limit 30 to (meta analysis or systematic reviews)
56	limit 34 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
57	limit 34 to (meta analysis or systematic reviews)
58	limit 38 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
59	limit 38 to (meta analysis or systematic reviews)
60	limit 42 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
61	limit 42 to (meta analysis or systematic reviews)
62	limit 49 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
63	limit 49 to (meta analysis or systematic reviews)
64	limit 53 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
65	limit 53 to (meta analysis or systematic reviews)
66	breast feeding.mp. or Breast Feeding/

Search No.	Search Syntax
67	18 and 66
68	67 not 17
69	68
70	limit 69 to (English language and humans and yr="1999–Current")
71	Pregnancy/
72	71 and 18
73	72 not 17
74	73
75	limit 74 to (English language and humans and yr="1999–Current")
76	limit 70 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
78	limit 70 to (meta analysis or systematic reviews)
80	limit 75 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
82	limit 75 to (meta analysis or systematic reviews)
Search No.	Search Syntax
Psychosocial	
1	marijuana.mp. or cannabis/
2	cannabis.mp.
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1–9
11	spice.ti,ab.
12	K2.ti,ab.
13	or/11–12
14	Rats/ or rats.ti,ab.
15	Mice/ or mice.ti,ab.
16	animals/ or animals.ti,ab.
17	or/14–16
18	10 not 13
19	psychosocial.mp. or Social Adjustment/
20	psychosocial effects.mp.
21	or/19–20

Search No.	Search Syntax
22	21 and 18
23	22 not 17
24	limit 23 to (English language and humans and yr="1999-Current")
25	cognitive development.mp.
26	Cognition/
27	Achievement/ or academic achievement.mp.
28	or/25-27
29	28 and 18
30	29 not 17
31	30
32	limit 31 to (English language and humans and yr="1999-Current")
33	cognitive impairment.mp. or Cognition Disorders/
34	33 and 18
35	34 not 17
36	limit 35 to (English language and humans and yr="1999-Current")
37	Employment/
38	Income/
39	or/37-38
40	39 and 18
41	40 not 17
42	limit 41 to (English language and humans and yr="1999-Current")
43	Interpersonal Relations/ or social relationships.mp.
44	43 and 18
45	44 not 17
46	45
47	limit 46 to (English language and humans and yr="1999-Current")
48	Social Behavior/ or social roles.mp.
49	48 and 18
50	49 not 17
51	limit 50 to (English language and humans and yr="1999-Current")
52	24 or 32 or 36 or 42 or 47 or 51
53	limit 52 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
54	24 or 32 or 36 or 42 or 47 or 51
55	limit 54 to (meta analysis or systematic reviews)
Search No.	Search Syntax
Respiratory	
1	marijuana.mp. or cannabis/
2	cannabis.mp.

Search No.	Search Syntax
3	cannabinoids.mp. or cannabinoid/
4	tetrahydrocannabinol.mp. or tetrahydrocannabinol/
5	dronabinol.mp. or dronabinol/
6	cannabidiol.mp. or cannabidiol/
7	cannabinol.mp. or cannabinol/
8	THC.mp.
9	marinol.mp.
10	or/1-9
11	spice.ti,ab.
12	K2.ti,ab.
13	or/11-12
14	10 not 13
15	Rats/ or rats.ti,ab.
16	Mice/ or mice.ti,ab.
17	animals/ or animals.ti,ab.
18	or/15-17
19	pulmonary.mp. or Pulmonary Disease, Chronic Obstructive/
20	lung disease.mp. or Lung Diseases/ or Respiratory Tract Diseases/ or respiratory disease.mp. or COPD.mp.
21	or/19-20
22	21 and 14
23	22 not 18
24	23
25	limit 24 to (human and English language and yr="1999-Current")
26	limit 25 to (meta analysis or systematic reviews)
27	limit 25 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)

Search 3

Date: July 6, 2016

Total citations:

Systematic Reviews: 912

Primary Literature: 6,286

Total: 7,198

Databases (search engine): Medline (Ovid); Embase (Ovid); Cochrane (Ovid)

Note: Ovid command-line syntax is provided below. Terms immediately followed by a forward slash (/) are Medical Subject Headings (MESH headings from MEDLINE) or EMTREE terms (from the EMBASE controlled vocabulary). The fields searched by a .mp in Embase and Medline include title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, and unique identifier. The fields searched by a .mp in Cochrane include title, short title, abstract, full text, keywords, caption text.

Search No.	Search Syntax
1	Cannabis/
2	Marijuana Smoking/
3	Marijuana Abuse/
4	Medical Marijuana/
5	Cannabinoids/
6	Dronabinol/
7	(cannabis or marijuana or cannabinoid or dronabinol or marinol). ti,ab.
8	THC.ti,ab
9	or/1-8
10	k2.ti,ab.
11	spice.ti,ab.
12	or/10-11
13	9 not 12
14	Mice/ or mice.ti,ab.
15	Rats/ or rats.ti,ab.
16	or/14-15
17	13 not 16
18	17
19	limit 18 to (English language and humans)
20	limit 19 to (classical article or clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or comparative study or controlled clinical trial or evaluation studies or guideline or journal article or multicenter study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or validation studies)

Search No.	Search Syntax
21	limit 19 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, NIH or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or editorial or english abstract or festschrift or government publications or historical article or in vitro or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or meta analysis or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or published erratum or research support, non us gov't or retracted publication or "retraction of publication" or "review" or "scientific integrity review" or systematic reviews or technical report or video-audio media or webcasts)
22	20 not 21
23	limit 22 to yr=1999-current
24	limit 19 to (meta analysis or "review" or systematic reviews)
25	limit 19 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, NIH or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or editorial or english abstract or festschrift or government publications or historical article or in vitro or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or published erratum or research support, non us gov't or retracted publication or "retraction of publication" or "scientific integrity review" or technical report or video-audio media or webcasts)
26	24 not 25
27	limit 26 to yr=1999-current

Search 4

Date: July 8, 2016

Total citations:

Systematic Reviews: 20

Primary Literature: 1,376

Total: 1,396

Database (search engine): PsycINFO (ProQuest)

Note: Terms with SU in front of them are Subject Headings taken from the Thesaurus of Psychological Index Terms.

Search	Search Syntax
Systematic Reviews + Meta Analysis	((SU("Cannabinoids" OR "Cannabis" OR "Marijuana Usage" OR "Marijuana") OR TI,AB(cannabis OR marijuana OR cannabinoid OR dronabinol) NOT TI,AB("K-2" OR spice)) AND peer(yes) AND (la.exact("ENG"))) AND (me.exact(("Systematic Review" OR "Meta Analysis") NOT ("Empirical Study" OR "Quantitative Study" OR "Interview" OR "Longitudinal Study" OR "Followup Study" OR "Prospective Study" OR "Literature Review" OR "Treatment Outcome/Clinical Trial" OR "Qualitative Study" OR "Brain Imaging" OR "Clinical Case Study" OR "Retrospective Study" OR "Mathematical Model" OR "Twin Study" OR "Focus Group" OR "Field Study" OR "Experimental Replication" OR "Scientific Simulation" OR "Nonclinical Case Study"))) AND rtype.exact(("Journal" OR "Peer-reviewed Journal" OR "Journal Article") NOT ("Comment/reply" OR "Editorial" OR "Letter" OR "Erratum/correction" OR "Review-book" OR "Column/opinion" OR "Abstract Collection" OR "Reprint" OR "Review-media" OR "Obituary")) AND po.exact(("Male" OR "Human" OR "Female" OR "Outpatient" OR "Inpatient") NOT "Animal") AND pd(19990101-20161231) AND PEER(yes))
Peer-reviewed Literature	(SU("Cannabinoids" OR "Cannabis" OR "Marijuana Usage" OR "Marijuana") OR TI(cannabis OR marijuana OR cannabinoid OR dronabinol) NOT TI,AB("K-2" OR spice)) AND peer(yes) AND (la.exact("ENG") AND me.exact(("Empirical Study" OR "Quantitative Study" OR "Longitudinal Study" OR "Followup Study" OR "Prospective Study" OR "Treatment Outcome/Clinical Trial" OR "Clinical Case Study" OR "Twin Study") NOT ("Interview" OR "Literature Review" OR "Qualitative Study" OR "Brain Imaging" OR "Mathematical Model" OR "Systematic Review" OR "Meta Analysis" OR "Field Study" OR "Focus Group"))) AND rtype.exact(("Journal" OR "Peer-reviewed Journal" OR "Journal Article") NOT ("Comment/reply" OR "Editorial" OR "Letter" OR "Erratum/correction" OR "Review-book" OR "Column/opinion" OR "Abstract Collection" OR "Reprint" OR "Review-media" OR "Obituary")) AND pd(19990101-20160601)

Search 5

Date: July 15, 2016

Total citations:

Systematic Reviews: 10

Primary Literature: 23

Total: 33

Database (search engine): Medline (Ovid); Embase (Ovid); Cochrane (Ovid)

Note: Ovid command-line syntax is provided below. Terms immediately followed by a forward slash (/) are Medical Subject Headings (MESH headings from MEDLINE) or EMTREE terms (from the EMBASE controlled vocabulary). The fields searched by a .mp in Embase and Medline include title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, and unique identifier. The fields searched by a .mp in Cochrane include title, short title, abstract, full text, keywords, caption text.

Search No.	Search Syntax
1	nabilone.mp
2	spice.ti,ab.
3	K2.ti,ab.
4	or/2-3
5	1 not 4
6	Rats/ or rats.ti,ab.
7	Mice/ or mice.ti,ab.
8	animals/ or animals.ti,ab.
9	or/6-8
10	5 not 9
11	limit 10 to (English language and yr="1999-Current")
12	limit 11 to (clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or observational study or randomized controlled trial)
13	limit 11 to (meta-analysis or systematic reviews)

Search 6

Date: August 2, 2016

Search Parameters: Published June 30, 2016–August 2, 2016

Total citations:

Systematic Reviews: 32

Primary Literature: 357

Total: 389

Database (search engine): Embase (Ovid)

Note: The Medline search was duplicated in PubMed to ensure that all e-pub and non-indexed / in-process citations were captured.

**Epub Ahead of Print, In-Process, and Other Non-Indexed Citations, Ovid
MEDLINE(R) Daily, and Ovid MEDLINE(R), 1946 to Present**

Search No.	Search Syntax
1	Cannabis/
2	Marijuana Smoking/
3	Marijuana Abuse/
4	Medical Marijuana/
5	Cannabinoids/
6	Dronabinol/
7	(cannabis or marijuana or cannabinoid or dronabinol or marinol). ti,ab.
8	nabilone.ti,ab.
9	or/1-8
10	k2.ti,ab.
11	spice.ti,ab.
12	or/10-11
13	9 not 12
14	Mice/ or mice.ti,ab.
15	Rats/ or rats.ti,ab.
16	or/14-15
17	13 not 16
18	17
19	limit 18 to (English language and humans)
20	limit 19 to (classical article or clinical study or clinical trial, all or clinical trial, phase I or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV or clinical trial or comparative study or controlled clinical trial or evaluation studies or guideline or journal article or multicenter study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or validation studies)
21	limit 19 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, NIH or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or editorial or English abstract or festschrift or government publications or historical article or in vitro or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or meta analysis or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or published erratum or research support, non us gov't or retracted publication or "retraction of publication" or "review" or "scientific integrity review" or systematic reviews or technical report or video-audio media or webcasts)
22	20 not 21
23	limit 22 to ed=20160630-20160901

Search No.	Search Syntax
24	limit 19 to (meta-analysis or "review" or systematic reviews)
25	limit 19 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, NIH or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or editorial or English abstract or festschrift or government publications or historical article or in vitro or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or published erratum or research support, non us gov't or retracted publication or "retraction of publication" or "scientific integrity review" or technical report or video-audio media or webcasts)
26	24 not 25
27	limit 26 to ed=20160630-20160901

Embase (Ovid)

Search No.	Search Syntax
1	major clinical study/
2	clinical article/
3	case report/
4	clinical trial/
5	controlled clinical trial/
6	phase 1 clinical trial/
7	phase 2 clinical trial/
8	phase 3 clinical trial/
9	phase 4 clinical trial/
10	randomized controlled trial/
11	double blind procedure/
12	single blind procedure/
13	crossover procedure/
14	multicenter study/
15	controlled study/
16	"clinical trial (topic)"/
17	"controlled clinical trial (topic)"/
18	"phase 1 clinical trial (topic)"/
19	"phase 2 clinical trial (topic)"/
20	"phase 3 clinical trial (topic)"/
21	"phase 4 clinical trial (topic)"/
22	"randomized controlled trial (topic)"/
23	"multicenter study (topic)"/
24	cannabis/

Search No.	Search Syntax
25	cannabis addiction/ or medical cannabis/ or "cannabis use"/ or cannabis smoking/ or cannabis derivative/
26	cannabinoid/
27	dronabinol/
28	nabilone/
29	(Cannabis or marijuana or cannabinoid or dronabinol or nabilone or marinol).ti,ab.
30	or/24-29
31	k2.ti,ab.
32	spice.ti,ab.
33	or/31-32
34	30 not 33
35	Mice/ or mice.ti,ab.
36	Rats/ or rats.ti,ab.
37	or/35-36
38	34 not 37
39	or/1-23
40	38 and 39
41	limit 40 to (journal and article)
42	limit 40 to (book or book series or chapter or conference abstract or conference paper or conference proceeding or "conference review" or editorial or erratum or letter or note or "review" or short survey or trade journal)
43	41 not 42
44	case report/
45	43 not 44
46	45
47	limit 46 to (human and English language)
48	limit 47 to yr="2016-Current"
49	limit 48 to dd=20160630-20161231
50	meta analysis/
51	"meta analysis (topic)"/
52	"meta analysis (topic)"/
53	"systematic review (topic)"/
54	or/50-53
55	38 and 54
56	limit 55 to (journal and (article or review))
57	56
58	limit 57 to (human and English language)
59	58
60	limit 59 to yr="2016-Current"
61	limit 60 to dd=20160630-20161231

REFERENCES

- Higgins, J. P. T., D. G. Altman, P. C. Gøtzsche, P. Jüni, D. Moher, A. D. Oxman, J. Savovic, K. F. Schulz, L. Weeks, J. A. Sterne, the Cochrane Bias Methods Group, and the Cochrane Statistical Methods Group. 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343:d5928. doi:10.1136/bmj.d5928.
- Wells, G. A., B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, P. Tugwell. 2011. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [http:// www. ohri.ca/programs/clinical_ epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) (accessed November 28, 2016).

Appendix C

Systematic Reviews

THERAPEUTIC EFFECTS OF CANNABIS AND CANNABINOIDS

Chronic Pain

- Andreae, M. H., G. M. Carter, N. Shaparin, K. Suslov, R. J. Ellis, M. A. Ware, D. I. Abrams, H. Prasad, B. Wilsey, D. Indyk, M. Johnson, and H. S. Sacks. 2015. Inhaled cannabis for chronic neuropathic pain: A meta-analysis of individual patient data. *Journal of Pain* 16(12):1121–1232.
- Fitzcharles, M. A., P. A. Ste-Marie, W. Hauser, D. J. Clauw, S. Jamal, J. Karsh, T. Landry, S. LeClercq, J. J. McDougall, Y. Shir, K. Shojania, and Z. Walsh. 2016. Efficacy, tolerability, and safety of cannabinoid treatments in the rheumatic diseases: A systematic review of randomized controlled trials. *Arthritis Care and Research* 68(5):681–688.
- Richards, B. L., S. L. Whittle, D. M. Van Der Heijde, and R. Buchbinder. 2012. Efficacy and safety of neuromodulators in inflammatory arthritis: A Cochrane systematic review. *Journal of Rheumatology* 39(Suppl 90):28–33.
- Snedecor, S. J., L. Sudharshan, J. C. Cappelleri, A. Sadosky, P. Desai, Y. J. Jalundhwala, and M. Botteman. 2013. Systematic review and comparison of pharmacologic therapies for neuropathic pain associated with spinal cord injury. *Journal of Pain Research* 6:539–547.
- Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidtkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Cancer

- Rocha, F., J. dos Santos Junior, S. Stefano, and D. da Silveira. 2014. Systematic review of the literature on clinical and experimental trials on the antitumor effects of cannabinoids in gliomas. *Journal of Neuro-Oncology* 116(1):11–24.

Chemotherapy-Induced Nausea and Vomiting

- Phillips, R. S., A. J. Friend, F. Gibson, E. Houghton, S. Gopaul, J. V. Craig, and B. Pizer. 2016. Antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood. *Cochrane Database of Systematic Reviews* 2:CD007786.
- Smith, L. A., F. Azariah, T. C. V. Lavender, N. S. Stoner, and S. Bettiol. 2015. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. *Cochrane Database of Systematic Reviews* 11:CD009464.
- Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidtkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Anorexia and Weight Loss

- Lutge, E. E., A. Gray, and N. Siegfried. 2013. The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. *Cochrane Database of Systematic Reviews* 4:CD005175.
- Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidtkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Irritable Bowel Syndrome (IBS)

The committee did not identify any good- or fair-quality systematic reviews that reported on IBS.

Epilepsy

- Gloss, D., and B. Vickrey. 2014. Cannabinoids for epilepsy. *Cochrane Database of Systematic Reviews* 3:CD009270.
- Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.

Spasticity Associated with Multiple Sclerosis and Paraplegia Caused by Spinal Cord Injury

- Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.
- Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidtkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Tourette Syndrome

- Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.
- Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidtkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Amyotrophic Lateral Sclerosis (ALS)

The committee did not identify any good- or fair-quality systematic reviews that reported on ALS.

Huntington's Disease

- Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.

Parkinson's Disease

- Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.

Dystonia

- Koppel, B. S., J. C. Brust, T. Fife, J. Bronstein, S. Youssof, G. Gronseth, and D. Gloss. 2014. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17):1556–1563.

Dementia

- Krishnan, S., R. Cairns, and R. Howard. 2009. Cannabinoids for the treatment of dementia. *Cochrane Database of Systematic Reviews* 2:CD007204.
- van den Elsen, G. A. H., A. I. A. Ahmed, M. Lammers, C. Kramers, R. J. Verkes, M. A. van der Marck, and M. G. M. O. Rikkert. 2014. Efficacy and safety of medical cannabinoids in older subjects: A systematic review. *Ageing Research Reviews* 14(1):56–64.

Glaucoma

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidtkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Traumatic Brain Injury/Intracranial Hemorrhage

The committee did not identify any good- or fair-quality systematic reviews that reported on traumatic brain injury/intracranial hemorrhage.

Addiction

Marshall, K., L. Gowing, R. Ali, and B. Le Foll. 2014. Pharmacotherapies for cannabis dependence. *Cochrane Database of Systematic Reviews* 12:CD008940.

Prud'Homme, M., R. Cata, and D. Jutras-Aswad. 2015. Cannabidiol as an intervention for addictive behaviors: A systematic review of the evidence. *Substance Abuse: Research and Treatment* 9:33–38.

Anxiety

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidtkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Depression

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidtkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Sleep Disorders

Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidtkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

Posttraumatic Stress Disorder (PTSD)

The committee did not identify any good- or fair-quality systematic reviews that reported on PTSD.

Schizophrenia and Other Psychoses

- McLoughlin, B. C., J. A. Pushpa-Rajah, D. Gillies, J. Rathbone, H. Variend, E. Kalakouti, and K. Kyprianou. 2014. Cannabis and schizophrenia. *Cochrane Database of Systematic Reviews* 10:CD004837.
- Whiting, P. F., R. F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A. V. Hernandez, J. C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidtkofer, M. Westwood, and J. Kleijnen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313(24):2456–2473.

CANCER INCIDENCE

Lung Cancer

- Zhang, L. R., H. Morgenstern, S. Greenland, S.-C. Chang, P. Lazarus, M. D. Teare, P. J. Woll, I. Orlow, and B. Cox, on behalf of the Cannabis and Respiratory Disease Group of New Zealand, Y. Brhane, G. Liu, and R. J. Hung. 2015. Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium. *International Journal of Cancer* 136(4):894–903.

Head and Neck Cancers

- de Carvalho, M. F., M. R. Dourado, I. B. Fernandes, C. T. Araujo, A. T. Mesquita, and M. L. Ramos-Jorge. 2015. Head and neck cancer among marijuana users: A meta-analysis of matched case-control studies. *Archives of Oral Biology* 60(12):1750–1755.

Testicular Cancer

- Gurney, J., C. Shaw, J. Stanley, V. Signal, and D. Sarfati. 2015. Cannabis exposure and risk of testicular cancer: A systematic review and meta-analysis. *BMC Cancer* 15:897.

Esophageal Cancer

The committee did not identify any good- or fair-quality systematic reviews that reported on esophageal cancer.

Other Cancers in Adults

The committee did not identify any good- or fair-quality systematic reviews that reported on other cancers in adults.

Childhood Cancers

The committee did not identify any good- or fair-quality systematic reviews that reported on childhood cancers.

CARDIOMETABOLIC RISK

The committee did not identify any good- or fair-quality systematic reviews that reported on the health endpoints addressed in this chapter.

RESPIRATORY DISEASE

Pulmonary Function

Tetraault, J. M., K. Crothers, B. A. Moore, R. Mehra, J. Concato, and D. A. Fiellin. 2007. Effects of marijuana smoking on pulmonary function and respiratory complications: A systematic review. *Archives of Internal Medicine* 167:221–228.

Chronic Obstructive Pulmonary Disease

The committee did not identify any good- or fair-quality systematic reviews that reported on chronic obstructive pulmonary disease.

Respiratory Symptoms, Including Chronic Bronchitis

Tetraault, J. M., K. Crothers, B. A. Moore, R. Mehra, J. Concato, and D. A. Fiellin. 2007. Effects of marijuana smoking on pulmonary function and respiratory complications: A systematic review. *Archives of Internal Medicine* 167:221–228.

Asthma

Tetraault, J. M., K. Crothers, B. A. Moore, R. Mehra, J. Concato, and D. A. Fiellin. 2007. Effects of marijuana smoking on pulmonary function and respiratory complications: A systematic review. *Archives of Internal Medicine* 167:221–228.

IMMUNITY

The committee did not identify any good- or fair-quality systematic reviews that reported on the health endpoints addressed in this chapter.

INJURY AND DEATH

All-Cause Mortality

Calabria, B., L. Degenhardt, W. Hall, and M. Lynskey. 2010. Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. *Drug and Alcohol Review* 29(3):318–330.

Occupational Injury

The committee did not identify any good- or fair-quality systematic reviews that reported on occupational injury.

Motor Vehicle Crashes

- Asbridge, M., J. A. Hayden, and J. L. Cartwright. 2012. Acute cannabis consumption and motor vehicle collision risk: Systematic review of observational studies and meta-analysis. *BMJ* 344:e536.
- Calabria, B., L. Degenhardt, W. Hall, and M. Lynskey. 2010. Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. *Drug and Alcohol Review* 29(3):318–330.
- Elvik, R. 2013. Risk of road accident associated with the use of drugs: A systematic review and meta-analysis of evidence from epidemiological studies. *Accident Analysis & Prevention* 60:254–267.
- Hartman, R. L., and M. A. Huestis. 2013. Cannabis effects on driving skills. *Clinical Chemistry* 59(3):478–492.
- Li, M. C., J. E. Brady, C. J. DiMaggio, A. R. Lusardi, K. Y. Tzong, and G. Li. 2012. Marijuana use and motor vehicle crashes. *Epidemiologic Reviews* 34:65–72.
- Rogeberg, O., and R. Elvik. 2016. The effects of cannabis intoxication on motor vehicle collision revisited and revised. *Addiction* 111:1348–1359.

Overdose Injuries and Death

The committee did not identify any good- or fair-quality systematic reviews that reported on overdose injuries and death.

PRENATAL, PERINATAL, AND NEONATAL EXPOSURE TO CANNABIS

Pregnancy Complications for the Mother

- Gunn, J. K. L., C. B. Rosales, K. E. Center, A. Nunez, S. J. Gibson, C. Christ, and J. E. Ehiri. 2016. Prenatal exposure to cannabis and maternal and child health outcomes: A systematic review and meta-analysis. *BMJ Open* 6(4):e009986.

Fetal Growth and Development

- Gunn, J. K. L., C. B. Rosales, K. E. Center, A. Nunez, S. J. Gibson, C. Christ, and J. E. Ehiri. 2016. Prenatal exposure to cannabis and maternal and child health outcomes: A systematic review and meta-analysis. *BMJ Open* 6(4):e009986.

Neonatal Conditions

- Gunn, J. K. L., C. B. Rosales, K. E. Center, A. Nunez, S. J. Gibson, C. Christ, and J. E. Ehiri. 2016. Prenatal exposure to cannabis and maternal and child health outcomes: A systematic review and meta-analysis. *BMJ Open* 6(4):e009986.

Later Outcomes

The committee did not identify any good- or fair-quality systematic reviews that reported on later outcomes.

PSYCHOSOCIAL

Cognition

- Batalla, A., S. Bhattacharyya, M. Yucel, P. Fusar-Poli, J. A. Crippa, S. Nogue, M. Torrens, J. Pujol, M. Farre, and R. Martin-Santos. 2013. Structural and functional imaging studies in chronic cannabis users: A systematic review of adolescent and adult findings. *PLOS ONE* 8(2):e55821.
- Broyd, S. J., H. H. Van Hell, C. Beale, M. Yucel, and N. Solowij. 2016. Acute and chronic effects of cannabinoids on human cognition—A systematic review. *Biological Psychiatry* 79(7):557–567.
- Grant, I., R. Gonzalez, C. L. Carey, L. Natarajan, and T. Wolfson. 2003. Non-acute (residual) neurocognitive effects of cannabis use: A meta-analytic study. *Journal of the International Neuropsychological Society* 9:679–689.
- Martin-Santos, R., A. B. Fagundo, J. A. Crippa, Z. Atakan, S. Bhattacharyya, P. Allen, P. Fusar-Poli, S. Borgwardt, M. Seal, G. F. Busatto, and P. McGuire. 2010. Neuroimaging in Cannabis Use: A Systematic Review of the Literature. *Psychological Medicine* 40(3):383–398.
- Schreiner, A. M., and M. E. Dunn. 2012. Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: A meta-analysis. *Experimental and Clinical Psychopharmacology* 20(5):420–429.

Academic Achievement

- Macleod, J., R. Oakes, A. Copello, I. Crome, M. Egger, M. Hickman, T. Oppenkowski, H. Stokes-Lampard, and G. Davey Smith. 2004. Psychological and social sequelae of cannabis and other illicit drug use by young people: A systematic review of longitudinal, general population studies. *Lancet* 363(9421):1579–1588.

Employment and Income

The committee did not identify any good- or fair-quality systematic reviews that reported on employment and income.

Social Relationships and Other Social Roles

- Macleod, J., R. Oakes, A. Copello, I. Crome, M. Egger, M. Hickman, T. Oppenkowski, H. Stokes-Lampard, and G. Davey Smith. 2004. Psychological and social sequelae of cannabis and other illicit drug use by young people: A systematic review of longitudinal, general population studies. *Lancet* 363(9421):1579–1588.

MENTAL HEALTH

Schizophrenia and Other Psychoses

- Donoghue, K., and G. A. Doody. 2012. Effect of illegal substance use on cognitive function in individuals with a psychotic disorder: A review and meta-analysis. *Neuropsychology* 26(6):785–801.
- Large, M., S. Sharma, M. T. Compton, T. Slade, and O. Nielssen. 2011. Cannabis use and earlier onset of psychosis: A systematic meta-analysis. *Archives of General Psychiatry* 68(6):555–561.
- Marconi, A., M. Di Forti, C. M. Lewis, R. M. Murray, and E. Vassos. 2016. Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia Bulletin* 42(5):1262–1269.
- Moore, T. H., S. Zammit, A. Lingford-Hughes, T. R. Barnes, P. B. Jones, M. Burke, and G. Lewis. 2007. Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet* 370(9584):319–328.
- Myles, N., H. Newall, O. Nielssen, and M. Large. 2012. The association between cannabis use and earlier age at onset of schizophrenia and other psychoses: Meta-analysis of possible confounding factors. *Current Pharmaceutical Design* 18(32):5055–5069.
- Rabin, R. A., K. K. Zakzanis, and T. P. George. 2011. The effects of cannabis use on neurocognition in schizophrenia: A meta-analysis. *Schizophrenia Research* 128(1–3):111–116.
- Szoke, A., A. M. Galliot, J. R. Richard, A. Ferchiou, G. Baudin, M. Leboyer, and F. Schurhoff. 2014. Association between cannabis use and schizotypal dimensions—A meta-analysis of cross-sectional studies. *Psychiatry Research* 219(1):58–66.
- van der Meer, F. J., E. Velthorst, C. J. Meijer, M. W. Machielsen, and L. de Haan. 2012. Cannabis use in patients at clinical high risk of psychosis: Impact on prodromal symptoms and transition to psychosis. *Current Pharmaceutical Design* 18(32):5036–5044.
- Yucel, M., E. Bora, D. I. Lubman, N. Solowij, W. J. Brewer, S. M. Cotton, P. Conus, M. J. Takagi, A. Fornito, S. J. Wood, P. D. McGorry, and C. Pantelis. 2012. The impact of cannabis use on cognitive functioning in patients with schizophrenia: A meta-analysis of existing findings and new data in a first-episode sample. *Schizophrenia Bulletin* 38(2):316–330.
- Zammit, S., T. H. Moore, A. Lingford-Hughes, T. R. Barnes, P. B. Jones, M., Burke, and G. Lewis. 2008. Effects of cannabis use on outcomes of psychotic disorders: Systematic review. *British Journal of Psychiatry* 193(5):357–363.

Bipolar Disorder

- Gibbs, M., C. Winsper, S. Marwaha, E. Gilbert, M. Broome, and S. P. Singh. 2015. Cannabis use and mania symptoms: A systematic review and meta-analysis. *Journal of Affective Disorders* 171:39–47.

Depression

- Lev-Ran, S., B. Le Foll, K. McKenzie, T. P. George, and J. Rehm. 2013. Bipolar disorder and co-occurring cannabis use disorders: Characteristics, co-morbidities and clinical correlates. *Psychiatry Research* 209(3):459–465.
- Moore, T. H., S. Zammit, A. Lingford-Hughes, T. R. Barnes, P. B. Jones, M. Burke, and G. Lewis. 2007. Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet* 370(9584):319–328.

Suicide

Borges, G., C. L. Bagge, and R. Orozco. 2016. A literature review and meta-analyses of cannabis use and suicidality. *Journal of Affective Disorders* 195:63–74.

Moore, T. H., S. Zammit, A. Lingford-Hughes, T. R. Barnes, P. B. Jones, M. Burke, and G. Lewis. 2007. Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *Lancet* 370(9584):319–328.

Anxiety

Kedzior, K. K., and L. T. Laeber. 2014. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population—A meta-analysis of 31 studies. *BMC Psychiatry* 14:136.

Posttraumatic Stress Disorder (PTSD)

The committee did not identify any good- or fair-quality systematic reviews that reported on PTSD.

PROBLEM CANNABIS USE

Development of Problem Cannabis Use

The committee did not identify any good- or fair-quality systematic reviews that reported on the development of problem cannabis use.

Risk and Protective Factors for Developing Problem Cannabis Use

Humphreys, K. L., T. Eng, and S. S. Lee. 2013. Stimulant medication and substance use outcomes: A meta-analysis. *JAMA Psychiatry* 70(7):740–749.

Kedzior, K. K., and L. T. Laeber. 2014. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population—A meta-analysis of 31 studies. *BMC Psychiatry* 14:136.

Risk and Protective Factors for Severity and Persistence of Problem Cannabis Use

The committee did not identify any good- or fair-quality systematic reviews that reported on the risk and protective factors for severity and persistence of problem cannabis use.

ABUSE OF OTHER SUBSTANCES

The committee did not identify any good- or fair-quality systematic reviews that reported on abuse of other substances.

Appendix D

Public Session Agendas

COMMITTEE MEETING

June 23–24, 2016

Meeting Location

The National Academies' Keck Center
Room 106
500 Fifth Street, NW
Washington, DC 20001

OPEN SESSION AGENDA

The National Academies of Sciences, Engineering, and Medicine has been charged to appoint an ad hoc committee of experts to develop a comprehensive, in-depth review of existing evidence regarding the health effects of using marijuana and/or its constituents, as well as to identify both a short- and long-term research agenda focused on improving our understanding of the association of marijuana uses relevant to health outcomes.

Thank you for joining us at this meeting. If you have a continued interest in the progress of this study, please feel free to subscribe to our listserv, which can be accessed through our study's website: <http://nationalacademies.org/hmd/activities/publichealth/marijuanahealtheffects.aspx>.

- 1:15 p.m. Welcome, Introductions, and Opening Remarks
Marie McCormick, Committee Chair
- 1:30 p.m. Sponsor Briefing on the Statement of Task
- Remarks from Sponsor Organizations
 - Steve Gust, Ph.D.
National Institute on Drug Abuse
 - Debbie Winn, Ph.D.
National Cancer Institute

- Amy Cohn, Ph.D. (via WebEx)
Truth Initiative
- Question and Answer Session with Committee and Sponsors

2:30 p.m. Adjourn Open Session

COMMITTEE MEETING

August 18, 2016

1:00–4:00pm (EDT)

Meeting Location

The National Academies' Keck Center
Room 106
500 Fifth Street, NW
Washington, DC
20001

Registration for in-person or webcast attendance:

<http://www.surveygizmo.com/s3/2943914/>

Open-Session-Health-Effects-of-Marijuana

Please note that in-person seating is limited

OPEN SESSION AGENDA

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Thank you for joining us at this meeting. If you have a continued interest in the progress of this study, please feel free to subscribe to our listserv, which can be accessed through our study's website: <http://nationalacademies.org/hmd/activities/publichealth/marijuanahealththeffects.aspx>.

1:00 p.m. Welcome, Introductions, and Opening Remarks
Marie McCormick, Committee Chair

1:15 p.m. Panel Discussions:

Health Effects of Cannabis

Speakers:

- Dr. Leslie R. Walker-Harding (Chair, Department of Pediatrics, Penn State Health Milton S. Hershey Medical Center; Medical Director, Penn State Children's Hospital)
- Dr. Sheryl Ryan (Professor of Pediatrics, Yale School of Medicine; Chief, Section of Adolescent Medicine, Yale School of Medicine)
- Dr. Michael Van Dyke (Section Chief, Environmental Epidemiology and Occupational Health, Colorado Department of Public Health and Environment)
- Dr. Peggy van der Pol (Senior Researcher, The Trimbos Institute, Netherlands Institute for Mental Health and Addiction)

Health Impact of Interest: The Role of Cannabis Use in Motor Vehicle Accidents

Speaker:

- Dr. Richard Compton (Director, National Highway Traffic Safety Administration, Office of Behavioral Safety Research)

Therapeutic Effects of Cannabis

Speakers:

- Dr. Igor Grant (Professor and Chair of the Department of Psychiatry at the University of California, San Diego School of Medicine; Director, HIV Neurobehavioral Research Program)
- Dr. Sheryl Ryan (Professor of Pediatrics, Yale School of Medicine; Chief, Section of Adolescent Medicine, Yale School of Medicine)

3:45 p.m. Question and Answer Session

4:00 p.m. Adjourn Open Session

Appendix E

Biographical Sketches for Committee Members, Staff, Fellow, and Advisor

COMMITTEE MEMBERS

Marie C. McCormick, M.D., Sc.D. (Chair), is currently the Sumner and Esther Feldberg Professor of Maternal and Child Health in the Department of Social and Behavioral Sciences at the Harvard T.H. Chan School of Public Health and a professor of pediatrics at the Harvard Medical School, and she is also a senior associate for academic affairs in the Department of Neonatology at the Beth Israel Deaconess Medical Center. Dr. McCormick is a pediatrician with a second doctorate in health services research, with all of her postgraduate training done at Johns Hopkins. In 1987 she joined the faculty of the Department of Pediatrics at Harvard Medical School, and in 1991 she became a professor and the chair of the Department of Maternal and Child Health at the Harvard School of Public Health and a professor of pediatrics. Her research has focused on the effectiveness of perinatal and neonatal health services on the health of women and children with a particular concern in the outcomes of very premature infants. She has been a senior investigator on the evaluations of two national demonstration programs (the Robert Wood Johnson Foundation National Perinatal Regionalization Program and, currently, the federal Healthy Start Program). In addition, she has provided significant scientific input, in a variety of roles, to the design and conduct of Infant Health and Development Project, the largest multisite, randomized trial of early childhood educational intervention, in particular, serving as the principal investigator of the follow-up done at 18 years of age. She is a member of the National Academy of Medicine, among other organizations. Her work

on several committees, most notably the Immunization Safety Review Committee, has earned her the David Rall Medal for exceptional service.

Donald I. Abrams, M.D., is chief of the Hematology-Oncology Division at Zuckerberg San Francisco General Hospital and a professor of clinical medicine at the University of California, San Francisco (UCSF). He was one of the original clinician/investigators to recognize and define many early AIDS-related conditions. He has long been interested in clinical trials of complementary medicine interventions for human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) and cancer, including evaluations of medicinal cannabis. In 1997 he received funding from the National Institute on Drug Abuse to conduct a clinical trial of the short-term safety of cannabinoids in HIV infection. Subsequently he was granted funds by the University of California Center for Medicinal Cannabis Research to conduct studies of the effectiveness of cannabis in a number of clinical conditions. He completed a placebo-controlled study of smoked cannabis in patients with painful HIV-related peripheral neuropathy as well as a study evaluating vaporization as a smokeless delivery system for medicinal cannabis. His last National Institute on Drug Abuse-funded trial investigated the safety and pharmacokinetic interaction between vaporized cannabis and sustained-release opioid analgesics in patients with chronic pain. He is currently conducting a translational National Heart, Lung, and Blood Institute-funded trial investigating vaporized cannabis in patients with sickle cell disease. He received an A.B. in molecular biology from Brown University in 1972 and graduated from the Stanford University School of Medicine in 1977. After completing an internal medicine residency at the Kaiser Foundation Hospital in San Francisco, he became a fellow in hematology-oncology at UCSF, before joining the faculty. In 2004, he completed a distance learning fellowship in integrative medicine from the University of Arizona and has since been providing integrative oncology consultations at the UCSF Osher Center for Integrative Medicine.

Margarita Alegría, Ph.D., is the chief of the Disparities Research Unit at Massachusetts General Hospital and a professor in the Departments of Medicine and Psychiatry at Harvard Medical School. Dr. Alegría is currently the principal investigator (PI) of four National Institutes of Health (NIH)-funded research studies: International Latino Research Partnership; Effects of Social Context, Culture and Minority Status on Depression and Anxiety; Building Community Capacity for Disability Prevention for Minority Elders; and Mechanisms Underlying Racial/Ethnic Disparities in Mental Disorders. She is also the co-PI of a William T. Grant Foundation project titled Understanding the Experience of Majority and Minority Sta-

tus through Photovoice. Dr. Alegría has published more than 200 papers, editorials, intervention training manuals, and several book chapters on topics such as improvement of health care services delivery for diverse racial and ethnic populations, conceptual and methodological issues with multicultural populations, and ways to bring the community's perspective into the design and implementation of health services. In 2011, she was elected as a member of the National Academy of Medicine. The recipient of several awards, Dr. Alegría was recently selected as *El Planeta's* (Massachusetts's largest circulating Spanish-language newspaper) 2013's Powermeter 100 most influential people for the Hispanic community in Massachusetts. Dr. Alegría also received the 2016 Cynthia Lucero Latino Mental Health Award by William James College.

William Checkley, M.D., Ph.D., is an associate professor of medicine at the Johns Hopkins University School of Medicine and has a joint appointment in the Department of International Health at the Bloomberg School of Public Health. His areas of clinical expertise include epidemiology, pulmonary disease, and critical care medicine. Dr. Checkley also serves as the medical director for Johns Hopkins International. Dr. Checkley earned his M.D. from Northwestern University and received his Ph.D. from Johns Hopkins University. He completed his internal medicine residency training at Emory University and his fellowship training in pulmonary and critical care medicine at Johns Hopkins School of Medicine. His research interests include international lung health, epidemiology, mechanical ventilation, and acute lung injury. Dr. Checkley has been recognized by the National Institutes of Health with the 2007 Postdoctoral National Research Service Award and the 2009 Pathway to Independence Career Award. He is certified in pulmonary disease and internal medicine by the American Board of Internal Medicine.

R. Lorraine Collins, Ph.D., is a psychologist and professor of community health and health behavior and the associate dean for research at the State University of New York at Buffalo (UB) School of Public Health and Health Professions (SPHHP). For two decades she conducted research as a senior scientist at UB's Research Institute on Addictions before joining the SPHHP as associate dean for research in 2008. Dr. Collins's research interests include cognitive and behavioral approaches to the conceptualization, prevention, and treatment of addictive behaviors, particularly among emerging and young adults. Examples of her projects funded by the National Institutes of Health include a study to examine the combined use of alcohol and marijuana and a study of the use of technology in interventions to reduce marijuana use.

Ziva D. Cooper, Ph.D., is an associate professor of clinical neurobiology in the Department of Psychiatry at Columbia University Medical Center. Dr. Cooper's primary research focus is translational studies investigating the effects of abused drugs and how these effects differ between males and females. For nearly a decade, she has been building on her training in preclinical models of drug dependence and developing an expertise in human laboratory studies on cannabis, cannabinoids, opioids, and cocaine while maintaining research projects in animal models of substance use. Her current research investigates the direct neurobiological effects of emerging drugs of abuse, including synthetic cannabinoids (i.e., K2, Spice) in laboratory animals and the direct physiological and behavioral effects of cannabis and cannabinoids as they pertain to both their abuse potential and potential therapeutic effects in double-blind, placebo-controlled human laboratory studies.

Adre J. du Plessis, M.B.Ch.B., M.P.H., is the director of the Fetal Medicine Institute, the division chief of fetal and transitional medicine, and director of the Fetal Brain Program at Children's National Health System. In addition, Dr. Du Plessis is a professor of pediatrics and neurology at the George Washington University School of Medicine. Dr. Du Plessis is a leading international expert in the normal and abnormal development of the brain as well as the mechanisms of injury to the immature brain. His career-long research focus has been on the nervous system of the fetus and newborn, the hazards and mechanisms of injury, and the potential prevention of insult to the brain. Under his leadership, the Fetal Medicine Institute provides individualized and specialized care to patients during and after the baby's birth. Dr. Du Plessis received his M.B.Ch.B. from the University of Cape Town, South Africa. He trained in pediatrics at the University of Cape Town, South Africa, and at Penn State University. In addition, he trained in child neurology at the St. Louis and Boston Children's Hospitals.

Sarah Feldstein Ewing, Ph.D., is a professor at the Oregon Health and Science University. Dr. Feldstein Ewing is a licensed clinical child psychologist with more than a decade of experience using a variety of evidence-based approaches to prevent and intervene with adolescent health risk behavior, including alcohol use, cannabis use, and human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) risk behavior. At this time, her lab has enrolled more than 1,000 youth within large-scale clinical trials to evaluate the developmental fit and treatment outcomes for motivational interviewing, behavioral skills training, cognitive behavioral approaches, mindfulness, and contingency management. She has published widely regarding the developmental fit, neurocognitive

mechanisms, gender differences, and cross-cultural adaptation of these prevention and intervention approaches for this developmental stage. She has also developed a highly innovative National Institutes of Health-funded line of translational research, evaluating the connection between basic biological mechanisms (e.g., functional brain activation, brain structure, genetic factors) and youth health risk behavior (e.g., clinical symptoms, HIV risk behaviors, treatment outcomes). She has conducted this work with alcohol-abusing adolescents, cannabis-abusing adolescents, adolescents engaged in risky sex, and youths with a high body mass index. Ultimately, the goal of her laboratory is to employ translational studies to (1) determine the driving factors underlying successful treatment outcomes, (2) develop more efficacious interventions, and (3) evaluate the efficacy of interventions in order to improve health outcomes and reduce the current disparities for high-risk adolescents of all backgrounds.

Sean Hennessy, Pharm.D., Ph.D., is a professor of epidemiology and a professor of systems pharmacology and translational therapeutics at the University of Pennsylvania Perelman School of Medicine. His primary field of interest is pharmacoepidemiology, which is the study of the health effects of medications in populations.

Kent Hutchison, Ph.D., is a professor of psychology and neuroscience and the director of clinical training at the University of Colorado Boulder. He completed his Ph.D. in clinical psychology at Oklahoma State University and then subsequently completed an internship at Brown University, where he stayed as a postdoctoral fellow specializing in research on addiction from 1995 to 1998. After leaving Brown University, Dr. Hutchison accepted a faculty position at the University of Colorado Boulder. He was promoted to associate professor in 2002 and full professor in 2007. Dr. Hutchison moved to the Mind Research Network (MRN) in Albuquerque, New Mexico, to pursue a program of research combining neuroimaging, clinical outcomes, and genetics in 2007, where he served as the chief science officer for 2 years. In 2011 he returned to the University of Colorado to help set up the Intermountain Neuroimaging Consortium, which involves the operation of two identical magnetic resonance scanners, one in Albuquerque at MRN and one in Boulder at the University of Colorado. He continues to serve as a liaison between the two organizations. Dr. Hutchison has a long track record of funding from the National Institutes of Health and publications. His research combines neuroimaging, epigenetic, pharmacological, and clinical perspectives. Recently he has focused on how inflammatory processes that result from alcohol abuse may damage important executive control circuits in the brain, ultimately contributing to loss of control over alcohol use. In large

part because of the change in Colorado law legalizing cannabis, he has also become very interested in cannabinoids and has launched several studies to gather data about the effects of cannabis with different ratios of tetrahydrocannabinol to cannabidiol on a variety of measures, including measures related to cognitive function and immune system inflammation.

Norbert E. Kaminski, Ph.D., is the director of the Institute for Integrative Toxicology and a professor of pharmacology and toxicology in the Cell and Molecular Biology Program at Michigan State University. Research being conducted in his laboratory is in the general areas of immunopharmacology and immunotoxicology and encompasses a number of extramurally funded projects. A major emphasis of all of these projects is the elucidation of the molecular mechanisms for the impairment of signal transduction cascades and gene expression during lymphocyte activation by drugs and chemicals. One major research focus is to characterize the mechanism for immune modulation by cannabinoid compounds. This effort has led to the first characterization of cannabinoid receptors within the immune system. Current goals include elucidation of signal transduction events initiated through—as well as independently of—cannabinoid receptors, including the peroxisome proliferator activated receptor (PPAR γ), leading to aberrant cytokine gene expression by T lymphocytes. A second major research focus is the characterization of the molecular mechanism responsible for altered B cell function produced by halogenated aromatic hydrocarbons, including dioxins and polychlorinated biphenols. This research, which resulted in the first characterization of the aryl hydrocarbon (AH) receptor and aryl hydrocarbon receptor nuclear translocator in B cells, has led to testing of the hypothesis that dioxin and dioxin-like compounds suppress antibody responses by impairing B cell differentiation in an AH receptor-dependent manner. A third area of his research concerns studies aimed at characterizing the role of cytokine expression patterns in airway remodeling induced by chemical and protein respiratory allergens as well as by respiratory pathogens.

Sachin Patel, M.D., Ph.D., is an associate professor of psychiatry and behavioral sciences and of molecular physiology and biophysics and director of the Division of Addiction Psychiatry at Vanderbilt University Medical Center. Dr. Patel's overall research goal is to understand the role of neuronal cannabinoid signaling in brain function relevant to psychiatric disorders. His lab has recently focused specifically on the role of the cannabinoid system in the regulation of stress response physiology and the subsequent development of anxiety and depressive phenotypes relevant to affective disorders. The lab is using animal models to examine the effects of adolescent stress exposure on the cannabinoid system and

cannabinoid-mediated synaptic plasticity in the amygdala, a key brain region implicated in affective disorders and developmental disorders, including autism. His lab is also interested in the role of cannabinoid signaling in modulating behavioral and synaptic alterations induced by very early life stress. Given that stress, especially early life stress, is associated with significantly higher rates of psychiatric disorders, including depression and posttraumatic stress disorder, understanding the cellular and molecular adaptations induced by stress exposure could provide opportunities for the development of novel therapeutic interventions for stress-related psychiatric disorders in children and adults. Another major focus of Dr. Patel's research is understanding the fundamental mechanisms of cannabinoid-mediated synaptic plasticity in the amygdala and how these forms of plasticity change during development. Understanding how the cannabinoid system modulates synaptic efficacy within emotional centers of the brain could provide mechanistic insight into developmental alterations induced by cannabis use during adolescence, which has been shown to be a risk factor for the development of psychiatric disorders, including schizophrenia. His lab is interested in understanding the mechanisms by which cannabis exposure early in life leads to an increased risk for the development of psychiatric disorders during adulthood.

Daniele Piomelli, Ph.D., is a professor of anatomy and neurobiology, has joint appointments in biological chemistry and pharmacology, and holds the Louise Turner Arnold Chair in Neurosciences at the University of California, Irvine (UCI), School of Medicine. Dr. Piomelli was trained in neuroscience and pharmacology. Research in his lab is focused on the function of lipid-derived messengers, with particular emphasis on the endogenous cannabinoids anandamide and 2-arachidonoylglycerol. Current research efforts converge on three areas: the formation and deactivation of anandamide and 2-arachidonoylglycerol; physiological roles of the endogenous cannabinoid system; and development of therapeutic agents that target anandamide and 2-arachidonoylglycerol metabolism. Primary neural cell cultures and state-of-the-art analytical techniques such as liquid chromatography/mass-spectrometry are used to investigate the formation and deactivation of anandamide and 2-arachidonoylglycerol in brain cells. Protein purification and cloning approaches are employed to characterize the molecular mechanisms underlying these processes. Cellular pharmacology and medicinal chemistry, in collaboration with leading international labs, are used to identify pharmacological agents that interfere with various aspects of endogenous cannabinoid function, and their therapeutic potential is explored *in vitro* and *in vivo*.

Stephen Sidney, M.D., M.P.H., is the director of research clinics at the Division of Research, Kaiser Permanente Northern California, where he has been conducting epidemiological studies since 1982. He is certified by the American Board of Internal Medicine and is a fellow of the American Heart Association Council on Epidemiology and Prevention. Dr. Sidney's research interests include cardiovascular diseases, including stroke, physical activity and fitness, cognitive function, and obesity, with an emphasis on health disparities. He conducted a National Institute on Drug Abuse–funded study from 1991 to 1994 on health outcomes associated with marijuana use utilizing survey and health outcome data from Kaiser Permanente Northern California, a large integrated health care system. He is the principal investigator of the Oakland field center of National Heart, Lung, and Blood Institute–funded Cardiovascular Risk Development in Young Adults (CARDIA) study, an ongoing 30-year longitudinal study of cardiovascular risk and disease development in individuals who were 18–30 years old at baseline, which includes marijuana use data collected throughout the study period. Dr. Sidney has authored or co-authored more than 360 peer-reviewed scientific publications covering a diverse range of topics, primarily in the area of cardiovascular epidemiology and also including more than 20 articles regarding epidemiological aspects of cannabis use and health outcomes. He received a B.A. in mathematics from Yale University, an M.D. from the Stanford University School of Medicine, and an M.P.H. in epidemiology from the University of California, Berkeley, School of Public Health.

Robert B. Wallace, M.D., M.Sc., is the Irene Ensminger Stecher professor of epidemiology and internal medicine at the University of Iowa Colleges of Public Health and Medicine. He has a variety of public health experiences. He was an Epidemic Intelligence Service Officer with the Centers for Disease Control and Prevention. He has conducted many population health studies as well as clinical trials, focusing on the prevention and control of chronic illnesses and other disabling conditions of older persons. These have included neurological conditions, fracture, cancers, coronary disease, mental illnesses, and the health of older women. He has continuing experience with community interventions related to the prevention of falls and motor vehicle injuries in older persons. He was a member of the U.S. Preventive Services Task Force and the National Advisory Council on Aging of the National Institute on Aging (National Institutes of Health [NIH]). He is an elected member of the National Academy of Medicine and has been a past chair of National Academies of Sciences, Engineering, and Medicine's Board on Population Health and Public Health Practice and Board on the Health of Select Populations and he has had substantial experience with National Academies studies

and panels. He is currently involved in several actively funded research projects by NIH, including several related to nutritional issues.

John Wiley Williams, M.D., M.H.S., is a professor of medicine at Duke University Medical Center and a past recipient of the Veterans Affairs (VA) Health Services Career Development Award and a Robert Wood Johnson Foundation Generalist Faculty Scholar Award. He received his bachelor and M.D. degrees from the University of North Carolina. Dr. Williams completed residency training at the University of Iowa and a research fellowship at Duke University. He is a primary care internist who is trained in epidemiology, biostatistics, and literature synthesis. Dr. Williams's topical interests include depression, mental health services, dementia, and the implementation of best practices. He is scientific editor for the *NC Medical Journal* and a medical editor for the Foundation for Informed Medical Decision Making. Dr. Williams directs the Durham VA Evidence Synthesis Program and has led numerous systematic reviews, many focusing on mental health services. Dr. Williams is board certified in internal medicine and active in clinical practice and resident physician education at the Durham VA Medical Center.

STUDY STAFF, FELLOW, AND ADVISOR

Jennifer A. Cohen, M.P.H., is a program officer in the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine on the Board on Population Health and Public Health Practice. She received her undergraduate degree and her M.P.H. from the University of Maryland. Ms. Cohen has been involved with the National Academies committees that produced *Organ Procurement and Transplantation; Clearing the Air: Asthma and Indoor Air Exposures; Veterans and Agent Orange: Herbicide/Dioxin Exposure and Type 2 Diabetes; Veterans and Agent Orange: Update 2000; Veterans and Agent Orange: Herbicide/Dioxin Exposure and Acute Myelogenous Leukemia in the Children of Vietnam Veterans; Veterans and Agent Orange: Update 2004; Veterans and Agent Orange: Update 2006; Veterans and Agent Orange: Update 2008; Veterans and Agent Orange: Update 2010; Veterans and Agent Orange: Update 2012; Post-Vietnam Dioxin Exposure in Agent Orange-Contaminated C-123 Aircraft; and Veterans and Agent Orange: Update 2014*. She was also rapporteur for *Challenges and Successes in Reducing Health Disparities*.

Brownsyne Tucker Edmonds, M.D., M.S., M.P.H. (*Norman F. Grant/American Board of Obstetrics and Gynecology Fellow*) is an assistant professor in the Department of Obstetrics and Gynecology at the Indiana University School of Medicine. Originally from Atlanta, Georgia, she received

her undergraduate degree in Community Health and African American Studies at Brown University. She went on to receive her medical degree from Brown Medical School, and, concurrently, completed a master's in public health at the Harvard School of Public Health with a concentration in quantitative methods. Dr. Tucker Edmonds trained in obstetrics and gynecology at Duke University Medical Center, where she served as an administrative chief resident in her final year. She then entered the Robert Wood Johnson Foundation Clinical Scholars Program fellowship at the University of Pennsylvania, where she received health services research training and a master's in health policy research. Most recently, she completed a clinical ethics fellowship through the Indiana University Health Fairbanks Center for Medical Ethics. Her work currently focuses on communication and decision making in the management of periviable deliveries—when end-of-life decisions are made at the very beginning of life.

Kelsey Geiser, M.A., is a research associate with the Health and Medicine Division's Board on Population Health and Public Health Practice. Previously, she worked in the Division of Behavioral and Social Sciences and Education with the Board on Children, Youth, and Families on two consensus studies: *Parenting Matters: Supporting Parents of Children Ages 0–8* and *Preventing Bullying Through Science, Policy, and Practice*. Prior to her work at the National Academies, Ms. Geiser wrote for the Stanford News Service and worked in the Palo Alto district office of Congresswoman Anna Eshoo. She has a B.A. and an M.A. in history from Stanford University with a focus on the historical treatment of women's and family health issues.

Hope R. Hare, M.F.A., is the administrative assistant for the Board on Population Health and Public Health Practice. She keeps the board information updated, administers the twice-yearly board meeting, and provides support for the board director and staff. Ms. Hare has worked for the National Academies of Sciences, Engineering, and Medicine since 2001. She holds an M.F.A. from Cornell University.

Leigh Miles Jackson, Ph.D. (*Study Director*), is a senior program officer in the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine's Board on Population Health and Public Health Practice. Previously, she worked in the Division of Behavioral and Social Sciences and Education with the Board on Children, Youth, and Families. She has served as the study director for the Committee on the Use of Economic Evidence to Inform Investments in Children, Youth, and Families and as the program officer for the Roundtable on the

Communication and Use of Social and Behavioral Sciences. Prior to joining the National Academies, she was a developmental psychopathology and neurogenomics research fellow at Vanderbilt University, where she investigated the role of chronic sleep disturbance and specific epigenetic modifications on the health outcomes of adolescents. She has a bachelor's degree in chemistry from Wake Forest University and a Ph.D. in molecular and systems pharmacology from Emory University.

Rose Marie Martinez, Sc.D. (*Senior Board Director*), has been the director of the Health and Medicine Division's Board on Population Health and Public Health Practice since 1999. Prior to joining the National Academies of Sciences, Engineering, and Medicine, Dr. Martinez was a senior health researcher at Mathematica Policy Research (1995–1999), where she conducted research on the impact of health system change on the public health infrastructure, access to care for vulnerable populations, managed care, and the health care workforce. She is a former assistant director for health financing and policy with the U.S. General Accounting Office and served for 6 years directing research studies for the Regional Health Ministry of Madrid, Spain.

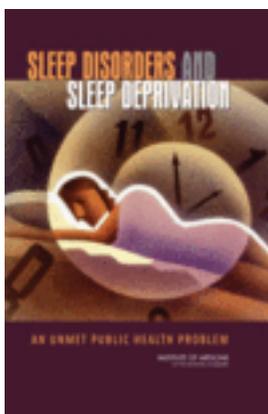
Matthew Masiello, is a research assistant for the Health and Medicine Division's Board on Population Health and Public Health Practice. He recently graduated from American University with a B.A. in international studies and a minor in public health. Prior to the working at the National Academies of Sciences, Engineering, and Medicine, he worked within several health-focused organizations, including the American Cancer Society and the Windber Research Institute.

Marjorie Pichon, is a senior program assistant for the Health and Medicine Division's Board on Population Health and Public Health Practice. While at the National Academies of Sciences, Engineering, and Medicine she has contributed to projects such as a National Strategy for the Elimination of Hepatitis B and C, Public Health Approaches to Reduce Vision Impairment and Promote Eye Health, and a workshop on Strategies to Improve Cardiac Arrest Survival. Prior to joining the National Academies, Ms. Pichon served as a Community Health Corps volunteer for Med-Star PromptCare, assisting underserved members of the community gain access to medical care. She graduated from Lewis & Clark College in May 2014 with a B.A. in psychology and a minor in rhetoric and media studies. During this time she collaborated on research in the college's Human Computer Interaction Lab studying how the structure of play influences creativity in children.

Kathleen Stratton, Ph.D. (*Advisor*), began her career at the National Academies of Sciences, Engineering and Medicine in 1990 in what was known at the time as the Institute of Medicine (IOM). She has spent most of her time with the Board on Population Health and Public Health Practice. She has staffed committees addressing vaccine safety and development, pandemic preparedness, environmental and occupational health, drug safety, Medicare payment programs, and tobacco control. She was given the IOM Cecil Research Award in 2002 for sustained contributions to vaccine safety and was made a staff scholar in 2005. After 2 years at The Pew Charitable Trusts working on U.S. Food and Drug Administration reform, she returned to the National Academies in Fall 2013. She received a B.A. in natural sciences from Johns Hopkins University and a Ph.D. in pharmacology and toxicology at the University of Maryland at Baltimore. She conducted postdoctoral research in the Department of Neuroscience at the Johns Hopkins School of Medicine.

Sara Tharakan, was a research associate for the Health and Medicine Division's Board on Population Health and Public Health Practice. While at the National Academies of Sciences, Engineering, and Medicine, she worked on a number of projects, including *Comprehensive Cancer Care for Children and Their Families: Summary of a Joint Workshop*; *Policy Issues in the Development and Adoption of Biomarkers for Molecularly Targeted Cancer Therapies: Workshop Summary*; and *Speech and Language Disorders in Children: Implications for the Social Security Administration's Supplemental Security Income Program*. Prior to joining the National Academies, she worked as an assistant researcher for the EKAM Foundation. Ms. Tharakan has a B.A. in political science and government from the University of North Carolina at Chapel Hill and is pursuing an M.Sc. at the London School of Economics and Political Science.

R. Brian Woodbury, is a research associate for the National Academies of Sciences, Engineering, and Medicine's Health and Medicine Division. Here he has contributed to projects on nurse credentialing research, health standards for long-duration and exploration spaceflight, public health approaches to reduce vision impairment and promote eye health, and treatment of cardiac arrest. Prior to his work at the National Academies, Mr. Woodbury served in the U.S. Army as a combat medic and licensed practical nurse, and he later co-founded and managed a public health-oriented developmental aid project in Nepal. Mr. Woodbury's academic background is in philosophy, classics, and the history and philosophy of mathematics and science at St. John's College, as well as premedical studies at Johns Hopkins University.



Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem

Harvey R. Colten and Bruce M. Altevogt, Editors,
Committee on Sleep Medicine and Research

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AN UNMET PUBLIC HEALTH PROBLEM

Committee on Sleep Medicine and Research

Board on Health Sciences Policy

Harvey R. Colten and Bruce M. Altevogt, *Editors*

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

*“Knowing is not enough; we must apply.
Willing is not enough; we must do.”*

—Goethe



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CLIFFORD B. SAPER, Harvard Medical School, Massachusetts

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BRUCE M. ALTEVOGT, Study Director
SARAH L. HANSON, Research Associate
DAVID CODREA, Financial Associate
AMY HAAS, Administrative Assistant
ELEANORE EDSON, Research Fellow
CATHARYN T. LIVERMAN, Senior Program Officer
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DAVID CODREA, Financial Associate

Independent Report Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Ruth Benca, Department of Psychiatry, University of Wisconsin, Madison

Mary A. Carskadon, Sleep Research Laboratory, Brown University

Norman H. Edelman, Health Sciences Center, SUNY Stony Brook

University

Stephen L. Hauser, Department of Neurology, University of California,
San Francisco

Meir H. Kryger, Sleep Disorders Center, St. Boniface General Hospital
Winnipeg, Manitoba, Canada

Lawrence S. Lewin, Executive Consultant, Chevy Chase, Maryland

Thomas Roth, Sleep Center, Henry Ford Hospital, Detroit, Michigan

Joan L. Shaver, College of Nursing, University of Illinois at Chicago

Joseph S. Takahashi, Department of Neurobiology & Physiology,
Northwestern University

Terry B. Young, Department of Population Health Sciences, University of Wisconsin

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **David J. Kupfer**, University of Pittsburgh School of Medicine, and **Floyd E. Bloom**, Professor Emeritus Department of Neuropharmacology, The Scripps Research Institute. Appointed by the National Research Council and Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

Sleep has been a subject of intense interest to poets and mystics and is found in folklore since antiquity. Only in the last half a century have scientists and physicians attempted a systematic study of the biology and disorders of sleep. Within the past four decades remarkable advances in the neurophysiology of normal sleep and in circadian biology and the discovery of the genes that regulate these biological rhythms have provided a scientific framework for the elucidation of the etiology, pathogenesis, and potential treatment of sleep disorders. These scientific advances and input from many clinical disciplines such as internal medicine, neurology, nursing, otolaryngology, pediatrics, psychiatry, psychology, and pulmonology have enriched the study and management of sleep pathology. However, the broad intellectual and service requirements for dealing with sleep has created difficulties in coordination and planning of research and clinical services. Recognition of around 90 distinct clinical disorders of sleep has created a platform and need for specialization in the study of sleep (somnology) and sleep pathology. Accordingly, professional societies such as the American Academy of Sleep Medicine, the American Sleep Apnea Association, the National Sleep Foundation, and the Sleep Research Society have been established and the discipline has been recognized by the American Board of Medical Specialties. Moreover, the National Institutes of Health (NIH) formed the National Center on Sleep Disorders Research (NCSDR) to coordinate research in sleep. Although these developments are positive, they do not yet fully address the scope and depth of the public and individual health consequences of sleep deprivation and sleep disorders. For example, more than 50 million Americans suffer a chronic sleep disorder and many others experience dis-

ruption of normal daytime activities owing to sleep deprivation. Sadly, the majority of individuals with substantial sleep disorders are not diagnosed and appropriately treated.

In recognition of the limited appreciation of the importance of sleep disorders and sleep deprivation for individuals and the public health, the American Academy of Sleep Medicine, the NCSDR at the NIH, the National Sleep Foundation, and the Sleep Research Society requested that the Institute of Medicine (IOM) do the following:

1. Review and quantify the public health significance of sleep health, sleep loss, and sleep disorders, including assessments of the contribution of sleep disorders to poor health, reduced quality of life, and early mortality, as well as the economic consequences of sleep loss and sleep disorders.
2. Identify gaps in the public health system relating to the understanding, management, and treatment of sleep loss and sleep disorders and assess the adequacy of the current resources and infrastructure for addressing the gaps.
3. Identify barriers to and opportunities for improving and stimulating multi- and interdisciplinary research and education in sleep medicine and biology. Delineate organizational models that will promote and facilitate sleep research in the basic sciences, collaborative research between basic scientists, clinicians, and population scientists in relevant specialties, and education of practitioners and scientists in sleep health, sleep disorders, and sleep research.
4. Develop a comprehensive plan for enhancing sleep medicine and sleep research for improving the public's health.

In response, the IOM appointed a 14-member committee with expertise in pulmonology, cardiology, nursing, neurology, pediatrics, adolescent medicine, psychiatry, epidemiology, public health, otolaryngology, academic and medical administration, and health sciences research. The committee met five times during the course of its work and held two workshops. In addition, the committee received input from relevant federal, private, and non-profit organizations.

Our findings confirmed the enormous public health burden of sleep disorders and sleep deprivation and the strikingly limited capacity of the health care enterprise to identify and treat the majority of individuals suffering sleep problems.

The direct effects of sleep disorders as well as the comorbidity with other substantial public health problems such as obesity, diabetes, stroke, and depression have a profound economic and social impact. Only minimal estimates of the economic impact of sleep disorders and their derivative consequences are possible because of underrecognition and underreporting.

At a minimum, however, the total direct and indirect cost of sleep disorders and sleep deprivation in the United States is hundreds of billions of dollars. The magnitude of the effect of sleep pathology is shocking even to experts in the field of somnology and sleep medicine. We found that there are too few professionals dedicated to sleep problems to meet the size and importance of the problem and there are too few educational programs that have the potential to increase the workforce of health care practitioners and scientists to meet even current demands. In addition, research that will advance our understanding of sleep pathology and its treatment has been underfunded. We therefore have outlined recommendations to address these shortcomings, in the hope that the burden of sleep disorders and sleep deprivation can be minimized. These recommendations fall into four broad categories: education (public, professional); technology; coordination of research initiatives at the NIH; and organization of research, clinical care, and education in academic health centers.

EDUCATION

The lack of public awareness should prompt a multimedia public education campaign that also targets elementary, middle, and high school students as well as undergraduate college health education programs about the impact of inadequate sleep.

Professional education will be enhanced by integrating the teaching of sleep medicine and biology into medical, nursing, and pharmacology curricula and into residency and specialty fellowships. Strategies to facilitate careers in somnology will be needed to meet the demand for sound science and expert clinical capacity to take care of the health problems related to sleep disorders.

TECHNOLOGY

The cumbersome nature and cost of diagnosis and treatment of sleep disorders and sleep loss will require research to develop and validate the efficacy of advances in diagnostic technologies, including ambulatory monitoring and imaging as well as the development of new therapeutic options for specific sleep disorders.

NATIONAL INSTITUTES OF HEALTH

The NCSDR at the NIH should take a more proactive role in promoting integration of research disciplines pertinent to somnology and sleep disorders, and it should promote training programs that increase the pipeline of highly qualified investigators. Together with other federal agencies, the

NCSDR can support increased public awareness and generation of more reliable prevalence data.

ORGANIZATION OF ACADEMIC HEALTH CENTERS

Within academic health centers new and existing sleep programs should be organized as Interdisciplinary Sleep Programs that encompass the relevant basic and clinical disciplines. The complexity of these programs will vary in accord with the capacity and goals of each center; therefore, we have proposed several different models. Networking among the most complex of these programs will facilitate research progress and accelerate implementation of new clinical strategies with help from the NCSDR.

The committee has been fortunate in having superb support from IOM staff and willing consultants in related fields. Without their help this report could not have been completed. We are most grateful.

Harvey R. Colten, M.D., *Chair*

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SLEEP DISORDERS AND SLEEP DEPRIVATION

AN UNMET PUBLIC HEALTH PROBLEM

Summary

ABSTRACT *It is estimated that 50 to 70 million Americans chronically suffer from a disorder of sleep and wakefulness, hindering daily functioning and adversely affecting health and longevity. The cumulative long-term effects of sleep deprivation and sleep disorders have been associated with a wide range of deleterious health consequences including an increased risk of hypertension, diabetes, obesity, depression, heart attack, and stroke. The Institute of Medicine (IOM) Committee on Sleep Medicine and Research concluded that although clinical activities and scientific opportunities in the field are expanding, awareness among the general public and health care professionals is low, given the magnitude of the burden. The available human resources and capacity are insufficient to further develop the science and to diagnose and treat individuals with sleep disorders. Therefore, the current situation necessitates a larger and more interdisciplinary workforce. Traditional scientific and medical disciplines need to be attracted into the somnology and sleep medicine field. Renewed and revitalized commitments to the field from the National Institutes of Health (NIH), academic health centers, private foundations, and professional societies are essential to ensure appropriate public and professional awareness, education and training, basic and clinical research, and patient care. Finally, the fragmentation of research and clinical care currently present in most academic institutions requires the creation of accredited interdisciplinary sleep programs in academic institutions.*

Fitful sleep, restless nights, and hitting the alarm clock button for an additional 10 minutes of sleep are all too familiar manifestations of the interactions of life with one of the frontiers of science and clinical practice—somnology¹ and sleep medicine. It is estimated that 50 to 70 million Americans suffer from a chronic disorder of sleep and wakefulness, hindering daily functioning and adversely affecting health. Hundreds of billions of dollars a year are spent on direct medical costs associated with doctor visits, hospital services, prescriptions, and over-the-counter medications. Almost 20 percent of all serious car crash injuries in the general population are associated with driver sleepiness, independent of alcohol effects. However, given this burden, awareness among the general public and health care professionals is low. In addition, the current clinical and scientific workforce is not sufficient to diagnose and treat individuals with sleep disorders.

Six million individuals suffer moderate to severe obstructive sleep apnea, a disorder characterized by brief periods of recurrent cessation of breathing caused by airway obstruction. Chronic insomnia, which hampers a person's ability to fall or stay asleep, occurs in approximately 30 million Americans. Restless legs syndrome and periodic limb movement disorder are neurological conditions characterized by an irresistible urge to move the legs and nocturnal limb movements; they affect approximately 6 million individuals, making it one of the most common movement disorders.

The cumulative effects of sleep loss and sleep disorders have been associated with a wide range of deleterious health consequences including an increased risk of hypertension, diabetes, obesity, depression, heart attack, and stroke. At the same time, the majority of people with sleep disorders are yet to be diagnosed. Compared to healthy individuals, those suffering from sleep loss and sleep disorders are less productive, have an increased health care utilization, and have an increased likelihood of injury.

In 2003 the NIH National Center on Sleep Disorders Research (NCSDR) published a research plan, which contained a set of research priorities for the field. However, recognizing that continued scientific and clinical advances will require a new coordinated strategy to improve public awareness and strengthen the field of Somnology and Sleep Medicine, the American Academy of Sleep Medicine, the NCSDR at the NIH, the National Sleep Foundation, and the Sleep Research Society requested that the IOM conduct a study that would examine: (1) the public health significance of sleep, sleep loss, and sleep disorders, (2) gaps in the public health system and adequacy

¹Somnology is the branch of science devoted to the study of the physiology of sleep, the behavioral dimensions of sleep, and the consequences of sleep loss and sleep disorders on an individual's and the general population's health, performance, safety, and quality of life. Sleep medicine is the branch of clinical medicine devoted to the diagnosis and treatment of individuals suffering from chronic sleep loss or sleep disorders.

of the current resources and infrastructures for addressing the gaps, (3) barriers and opportunities for improving interdisciplinary research and medical education and training in the area of sleep and sleep medicine, and (4) develop a comprehensive plan for enhancing sleep medicine and sleep research.

In response to the request the IOM appointed a 14-member committee with expertise in academic and medical administration, adolescent medicine, cardiology, epidemiology, geriatrics, health sciences research, neurology, nursing, otolaryngology, pediatrics, psychiatry, and pulmonology. The committee met five times during the course of its work and held two workshops that provided input on: (1) the current public health burden of sleep loss and chronic sleep disorders, and (2) the organization and operation of various types of academic sleep programs.

This committee recognizes that with the continued leadership of the NCSDR and its advisory board a coordinated strategy, described below, is needed to ensure continued advances (Box ES-1). This strategy requires concurrent commitment to the following activities:

- Establish the workforce required to meet the clinical and scientific demands of the field.
- Increase awareness of the burden of sleep loss and sleep disorders among the general public.
- Improve surveillance and monitoring of the public health burden of sleep loss and sleep disorders.
- Expand awareness among health care professionals through education and training.
- Develop and validate new and existing diagnostic and therapeutic technologies.
- Expand accreditation criteria to emphasize treatment, long-term patient care, and chronic disease management strategies.
- Strengthen the national research infrastructure to connect individual investigators, research programs, and research centers.
- Increase the investment in interdisciplinary sleep programs in academic health centers that emphasize long-term clinical care, training, and research.

THE NATIONAL INSTITUTES OF HEALTH LEADERSHIP IN RESEARCH AND TRAINING

To a greater extent than most scientific and medical disciplines, the field of somnology and sleep medicine cuts across many clinical and basic research disciplines, including but not limited to cardiology, dentistry, endocrinology, epidemiology, geriatrics, molecular biology, neurology,

neuroscience, nursing, otolaryngology, pediatrics, pharmacology, psychiatry, psychology, and pulmonology. In 2004, there were 331 sleep-related research project grants sponsored by 17 institutes at the NIH. The NIH has two entities to coordinate its sleep-related activities, the Trans-NIH Sleep Research Coordinating Committee and the NCSDR. However, major challenges remain in involving all relevant NIH institutes, centers, and offices; developing a coordinated research and training program; and integrating the efforts of the NCSDR, its advisory board, and the Trans-NIH Sleep Research Coordinating Committee.

Investment in sleep-related research has grown dramatically over the past 10 years; however, the growth in research and training programs have not kept up with the rapid pace of scientific advances. At the same time that the science and magnitude of the problem requires greater investment, NIH funding to sleep-related activities is reaching a plateau. This has partially overlapped the period when the overall NIH budget has plateaued. Consequently, the future outlook for somnology and sleep medicine is unclear. In 2004, for the first time since the NCSR was established in 1993, there was a decrease in annual NIH expenditures for sleep-related programs, fewer research project grants were funded, and the number of new grants awarded decreased. Over the last three years the NCSDR has only sponsored two programs—one request for applications and one program announcement—a marked reduction since the inception of the NCSDR. This presents an even greater challenge for a field that requires growth in scientific workforce and technology. Thus, there must be incremental growth in this field to meet the public health and economic burden caused by sleep loss and sleep disorders. It is important that research priorities continue to be defined for both short- and long-term goals. To address this problem the committee makes the following recommendation.

Recommendation 8.1 The National Center on Sleep Disorders Research and its advisory board should play a more proactive role in stimulating and coordinating the field.

The National Center on Sleep Disorders and Research (NCSDR) should have adequate staff and resources to ensure its ability to fulfill its mission of coordinating and stimulating training, research, and health information dissemination relevant to somnology and sleep disorders. All relevant institutes with significant sleep portfolios should become members of the Trans-NIH Sleep Research Coordinating Committee. Further, the NCSDR Advisory Board should take a more proactive role in advising the director of the NCSDR. On an annual basis, the NCSDR and its advisory board should:

- Identify specific objectives that address each of the three NCSDR missions and evaluate specific actions taken to accomplish each objective. This assessment should be reported in an annual meeting to the NIH-Trans Sleep Coordinating Committee, the institute directors of its members, and to the director of the NIH.
- Directors of the other federal agencies that fund significant sleep-related activities, such as Department of Defense, Department of Commerce, Department of Education, Department of Labor, and Department of Transportation should report annually on their activities to the NCSDR Advisory Board.
- The NCSDR Advisory Board should annually review the current NIH portfolio of sleep-related grants, as well as requests for applications, and program announcements, assess them for responsiveness to the program plan and identify gaps in research and training.
- The NCSDR Advisory Board should annually recommend new, or modify existing, requests for applications that can be presented to appropriate NIH institutes and other federal agencies including the Centers for Disease Control and Prevention and Department of Defense. Multiple members of the Trans-NIH Sleep Coordinating Committee are encouraged to continue to cosponsor sleep-related grants.

ESTABLISHING A SUFFICIENT WORKFORCE

One of the most pressing needs recognized by this committee is to create an infrastructure capable of developing the workforce required to meet the clinical and scientific demands of the field. This will entail increased investment by the NIH, academia, professional societies, private foundations, and industry. In 2004 there were only 151 researchers who had a clinical sleep-related research project grant (R01), and only 126 investigators focused primarily on basic sleep-related research projects, a decrease from the number of R01 awards in 2003. Further, of the top academic institutions that received the greatest number of grants from the NIH, less than half had career development or training grants in somnology or sleep medicine. Only 54 doctorates were awarded with a focus on somnology or sleep medicine in 2004. This workforce is insufficient given the burden of sleep loss and sleep disorders.

The NIH support of career development awards has decreased. Over the period encompassing 2000 to 2004 there was a decrease in the number of career development awards. Further, since 1997 there have been no new requests for application (RFAs) or program announcements (PAs) for sleep-related fellowship (F), training (T), or career development (K) programs. Given

these statistics, creating an infrastructure to develop a workforce capable of meeting the clinical and scientific demand is a challenge for the field.

Compared to other fields the current number of clinicians and scientists in the field is not sufficient, given the public health burden of sleep loss and sleep disorders. Further, NIH, academia, and private foundations have not sufficiently supported the development of an adequate workforce. To strengthen the interdisciplinary aspect of the field it is not only important to attract new investigators to the field, but also to expand the number of trained scientists in other relevant disciplines electing to focus on sleep-related research. Therefore, the committee makes the following recommendation designed to improve training and mentoring activities.

Recommendation 7.1: The National Institutes of Health and private foundations should increase investment in interdisciplinary somnology and sleep medicine research training and mentoring activities.

The National Institutes of Health, foundations, and professional societies should utilize and develop further funding mechanisms to attract young investigators into the field of somnology and sleep medicine. As a reflection of the interdisciplinary nature of somnology and sleep medicine, members of the Trans-NIH Sleep Research Coordinating Committee should be encouraged to combine resources to sponsor grants for disciplinary and cross-disciplinary training and mentoring activities (T, F, and K funding mechanisms) of medical students, graduate students, postdoctoral fellows, clinical fellows, and junior faculty.

To implement this recommendation the following should be considered:

- The Trans-NIH Sleep Research Coordinating Committee should establish a somnology and sleep medicine career development program. This program should support trainees for a significant number of years, spanning research training in fellowship and research career development as a faculty member. It should also facilitate midcareer training opportunities (e.g., K21, K24), the Academic Career Award for Education and Curriculum Development program (K07), and research education grants (R25).
- Existing training grants or large research programs in disciplines related to somnology or sleep medicine (e.g., internal medicine, neurology, psychiatry, psychology, otolaryngology, nursing, epidemiology, neuroscience, health services research) should allow for the addition of a sleep medicine trainee. Where pertinent expertise is not available on-site, remote mentoring at other institutions should be encouraged.

PUBLIC AND PROFESSIONAL AWARENESS

A well-coordinated strategy to improve sleep-related health care is required, owing to the public health burden of sleep loss and sleep disorders coupled with the low awareness among the general population, health care professionals, professional societies, and policy makers. Increasing the awareness and improving the diagnosis and treatment of sleep disorders requires a multipronged effort that includes three key components: public education, surveillance and monitoring of the burden of sleep loss and sleep disorders, and training for health professionals. The preeminent goal of these activities is to create and sustain a broad societal commitment to adopting proper sleep habits as a primary tenet of health. Such a commitment will require participation by those individuals and organizations in a position to educate the public at national, state, local, and community levels—including K–12 education, colleges and universities, medical schools, nursing schools, hospitals, community clinics, local health departments, private industry, and entertainment media. This will necessitate simultaneous investment in public education campaigns for all age groups and a sustained effort to integrate sleep-related content into curricula of undergraduate education.

Recommendation 5.1: The National Center on Sleep Disorders Research and the Centers for Disease Control and Prevention should establish a multimedia public education campaign.

The National Center on Sleep Disorders Research—working with the Centers for Disease Control and Prevention, the proposed National Somnology and Sleep Medicine Research Network, private organizations and foundations, entertainment and news media, and private industry—should develop, implement, and evaluate a long-term national multimedia and public awareness campaign directed to targeted segments of the population (e.g., children, their parents, and teachers in preschool and elementary school; adolescents; college students and young adults; middle-aged adults; and elderly people) and specific high-risk populations (e.g., minorities).

Improve Surveillance and Monitoring of the Public Health Burden

Adequate public health education not only requires informing public and health care practitioners, but also adequate monitoring of the public health burden. The development of adequate surveillance and monitoring systems is important for informing policy makers, health care providers,

researchers, and the public about the effectiveness of health care services, programs, rules and regulations, and policies. However, there is currently very little ongoing nationwide surveillance. Thus existing national and state-wide databases should be amended to allow for improved surveillance and monitoring of the burden of sleep loss and sleep disorders in the United States population.

Recommendation 5.3: The Centers for Disease Control and Prevention and National Center on Sleep Disorders Research should support additional surveillance and monitoring of sleep patterns and sleep disorders.

The Centers for Disease Control and Prevention, working with the National Center on Sleep Disorders Research, should support the development and expansion of adequate surveillance and monitoring instruments designed to examine the American population's sleep patterns and the prevalence and health outcomes associated with sleep disorders.

Increasing Awareness Among Health Professionals

Increasing education and training of health care professionals in somnology and sleep medicine will improve the awareness of the associated public health burden and attract a new pool of clinicians and scientists interested in the field. Time devoted to sleep-related material in health and life sciences curricula is inadequate given the magnitude of the morbid effects that sleep disorders have on the most common diseases (e.g. obesity, hypertension, heart attack, and diabetes) and accidents. Focused training about sleep can positively influence the performance of health care providers. In particular, medical, nursing, dentistry, and pharmacy students require greater exposure to the public health burden of sleep loss and sleep disorders. Thus the committee makes the following recommendation to increase sleep-related content in health sciences curricula.

Recommendation 5.2: Academic health centers should integrate the teaching of somnology and sleep medicine into baccalaureate and doctoral health sciences programs, as well as residency and fellowship training and continuing professional development programs.

The subjects of sleep loss and sleep disorders should be included in the curricula of relevant baccalaureate and graduate educational

and research programs of all the health sciences. Similarly, post-graduate, residency, and fellowship training programs, as well as continuing professional development programs, must include this content. The curriculum should expose students in the fields of medicine and allied health fields to the etiology, pathophysiology, diagnosis, treatment, prevention, and public health burden of sleep loss and sleep disorders. Relevant accrediting bodies and licensing boards ought to define sleep-related curriculum requirements and expectations for knowledge and competency (e.g., Liaison Committee on Medical Education, Accreditation Council for Graduate Medical Education, American Board of Medical Specialties, the National League for Nursing, the Commission on Collegiate Nursing Education, and the Council on Education for Public Health). Further, a means for credentialing nonphysicians should be maintained by the American Board of Sleep Medicine, or new mechanisms should be developed by relevant organizations.

TECHNOLOGY DEVELOPMENT AND ACCREDITATION

As awareness increases, greater investment in the development and validation of new and existing diagnostic and therapeutic technologies is required to meet the anticipated demand. Today, the capacity needed to serve the population seeking diagnosis and treatment is inadequate. The wait time for a polysomnogram, the procedure used to diagnose sleep disorders, can be up to 10 weeks. Most American communities do not have adequate health care resources to meet the clinical demand; therefore, millions of individuals suffering from sleep disorders remain undiagnosed and untreated. It has been estimated that sleep apnea alone, a diagnosis that necessitates polysomnography to meet current criteria set out by third-party payers, annually requires at least 2,300 polysomnograms per 100,000 population. However, on average, only 425 polysomnograms per 100,000 population are performed each year in the United States, a level far below the need. In fact, 33 states perform fewer than 500 polysomnograms per 100,000 people annually. This shortfall will exacerbate as awareness of the clinical consequences and public health burden of sleep loss and disorders increases, particularly with the aging of the United States population. Given the cumbersome nature and cost of the diagnosis and treatment of sleep disorders and sleep loss and the resultant inequities with regard to access, in order to ensure future quality care the committee recommends greater investment in the development of new and validation of existing diagnostic and therapeutic technologies.

Recommendation 6.1: The National Institutes of Health and the Agency for Healthcare Research and Quality should support the validation and development of existing and new diagnostic and therapeutic technologies.

The National Center on Sleep Disorders Research—working with the Trans-NIH Sleep Research Coordinating Committee, the Agency for Health Care Policy and Research, other federal agencies, and private industry—should support the evaluation and validation of existing diagnostic and therapeutic technologies. Further, development of new technologies such as ambulatory monitoring, biological markers, and imaging techniques should be vigorously supported.

Establish Sleep Laboratories in the NIH Clinical Research Program

The intramural clinical research program at the NIH does not have a sleep laboratory. Consequently, many experimental sleep therapies and the relationship between sleep processes and disease development are not being examined. If there is adequate investment in extramural sleep-related programs, the field can continue to make great strides; therefore, the committee does not support use of limited resources to invest in an intramural somnology and sleep disorders research program. However, because appropriateness of sleep patterns is one of the basic tenets of health, the committee strongly urges the NIH intramural clinical research program to ascertain the need for establishing a sleep study laboratory so that evaluation of sleep may be integrated into ongoing relevant clinical research protocols at NIH.

Recommendation 8.3: The National Institutes of Health should ascertain the need for a transdisciplinary sleep laboratory that would serve as a core resource in its intramural clinical research program.

The Director of the National Institutes of Health Intramural Research Program should ascertain the need for a transdisciplinary sleep laboratory within the intramural clinical research program that would serve as a core resource for the community of intramural clinical investigators across all institutes.

Improved Accreditation Standards Are Required

Sleep disorders are chronic conditions frequently associated with other comorbidities (e.g., cardiovascular disease, depression, diabetes), which often require complex treatments. Despite the importance of early recognition and treatment, the primary focus of most existing sleep centers appears to be on diagnosis, rather than on comprehensive care of sleep loss and sleep disorders as chronic conditions. This narrow focus may largely be the unintended result of compliance with criteria for accreditation of sleep laboratories, which emphasize diagnostic standards and reimbursement, for diagnostic testing. To address this it is recommended that accreditation criteria for sleep centers, in which are imbedded sleep laboratories, be expanded to emphasize treatment, long-term patient care, and management strategies.

Recommendation 9.2: Sleep laboratories should be part of accredited sleep centers, the latter to include long-term strategies for patient care and chronic disease management.

All private and academic sleep laboratories should be under the auspices of accredited sleep centers and include adequate mechanisms to ensure long-term patient care and chronic disease management. Accreditation criteria should expand beyond a primary focus on diagnostic testing to emphasize treatment, long-term patient care, and chronic disease management strategies.

INTERDISCIPLINARY SLEEP PROGRAMS IN ACADEMIC HEALTH CENTERS

Accelerating Scientific Advances

A coordinated and integrated strategy requires bolstering clinical and basic research efforts, catalyzing collaborative research efforts, and attracting the breadth of talented researchers who can provide leadership to advance research and clinical care in sleep loss and sleep disorders. Key to accelerating progress in the treatment of chronic sleep loss and sleep disorders is the development of a coordinated, focused, and centralized network that connects individual investigators, research programs, and research centers; facilitates collaborative projects; encompasses relevant research from diverse fields; and builds on the unique strengths of each research effort to move toward effective therapy, prevention, and treatment. Somnology and Sleep Medicine Research Centers of Excellence would spearhead these translational research efforts and promote collaborations among all sites conducting research relevant to somnology and

sleep medicine. Similar to cancer centers, the Somnology and Sleep Medicine Centers of Excellence would act as local, regional, and national resources for the scientific community and the community at large. These centers would provide the interdisciplinary environment that is essential to accelerate the development of therapies for chronic sleep loss and sleep disorders. In addition, these centers would facilitate interactions among basic, clinical, and population-focused scientists. These would not only be research centers, but somnology and sleep medicine centers that emphasize the close association among research, clinical care, and education. The committee further envisions a sustained network for somnology and sleep medicine in the United States that would facilitate public education, career development opportunities, translational research, and implementation of multicenter clinical trials. Although in aggregate, sleep loss and sleep disorders are prevalent, among these are many rare conditions that would benefit from a national data collection system and clinical network.

Despite the limited size of the field, the committee believes that the somnology and sleep medicine field is now sufficiently mature for the establishment of a national somnology and sleep medicine research network. Scientific advances and a number of large academic interdisciplinary sleep programs place the proposed network in position to successfully compete for funding from the National Heart, Lung, and Blood Institute and other members of the Trans-NIH Sleep Research Coordinating Committee.

Recommendation 8.2: The National Institutes of Health should establish a National Somnology and Sleep Medicine Research Network.

The National Center on Sleep Disorders Research in collaboration with the Trans-NIH Sleep Research Coordination Committee should establish a National Somnology and Sleep Medicine Research Network. Type III regional interdisciplinary sleep programs designated by the National Institutes of Health would act as regional centers working with basic research laboratories and sleep cores at NIH-designated clinical translational research centers. It is envisioned that the networks would do the following:

- Coordinate and support the current and future cadre of basic and clinical researchers.
- Train new investigators and fellows.
- Provide core capabilities for basic, clinical, and translational research.
- Support multisite clinical research in children, adolescents, adults, and elderly.

- Create and support virtual networking centers to facilitate the standardization and sharing of data and resources online and enhance collaborations with researchers not working in research centers.
- Create a data coordinating center that includes an Internet-based clearing house for the publication of all data produced in cooperation with the research and clinical network.
- Together with the Agency for Healthcare Research and Quality develop standards for research, outcomes, and clinical practice.
- Work with the Center for Disease Control and Prevention to integrate and support surveillance and population-based research.

Criteria for Interdisciplinary Sleep Programs in Academic Health Centers

Somnology and sleep medicine is an emerging interdisciplinary field that is being forged from several disciplines and clinical specialties. However, the limited investment and organization of sleep programs in academic health centers do not favor interdisciplinary research efforts and continued advances in clinical care. Consequently, the committee recommends a three-tier model for interdisciplinary sleep programs, which lays down the guiding principles for their organization in all academic health centers—progressing from programs that emphasize clinical care and education to programs with a considerable capacity for research, advanced training, and public education (Table S-1). It is the belief of the committee that, if these components and guiding principles are followed, interdisciplinary sleep programs can thrive, whether as free-standing departments or as programs within an existing department, division, or unit.

Status as a Type I interdisciplinary sleep program is achievable by many academic health centers nationwide; it primarily focuses on clinical care. This type should highlight the importance of increasing awareness among health care professionals by offering educational programs for medical students and residents in primary care. The Type I interdisciplinary sleep program is a single accredited center that emphasizes a comprehensive diagnosis and treatment program.

A Type II interdisciplinary sleep program includes the characteristics of a Type I program but in addition is designed to provide optimal education, training, and research in somnology and sleep medicine for scientists and physicians, including an accredited sleep fellowship program for physicians. A Type III regional interdisciplinary sleep program includes the characteristics of Type I and II programs; however, this type of program would act as a regional coordinator for the proposed National Somnology and Sleep

Medicine Research Network for education, training, mentoring, clinical care, research, and clinical trials.

Recommendation 9.1: New and existing sleep programs in academic health centers should meet the criteria of a Type I, II, or III interdisciplinary sleep program.

New and existing sleep programs should at a minimum conform to the criteria of a Type I clinical interdisciplinary sleep program. Academic medical centers with a commitment to interdisciplinary training are encouraged to train sleep scientists and fellows in sleep medicine, which would require at least a Type II training and research interdisciplinary sleep program. Research-intensive medical centers should aspire to become Type III regional interdisciplinary sleep programs and coordinators of the National Somnology and Sleep Medicine Research Network. The American Academy of Sleep Medicine should develop accreditation criteria for sleep programs specific to academic health centers.

PRIORITIES TO ADVANCE SOMNOLOGY AND SLEEP MEDICINE

The field is particularly well suited to interdisciplinary and translational strategies. NIH's Roadmap identified a number of initiatives that aim to foster the development of interdisciplinary research and training. The growth of this field fits in with the framework of the Roadmap and thus could serve as a prototypical program for these new cross-institute initiatives.

Recognizing the current fiscal restraints at the NIH and the prerequisite requirements for the field, the committee recommends the following prioritized strategy. Of primary importance is

- improving awareness among the general public and health care professionals,
- increasing investment in interdisciplinary somnology and sleep medicine research training and mentoring activities,
- validating and developing new and existing technologies for diagnosis and treatment.

Transforming academic health centers is also an important part of the strategy. Although many health centers have the components to establish interdisciplinary sleep programs, many do not, and it will take time and energy to develop successful programs. Therefore, it is important that academia and accrediting bodies begin facilitating this transformation.

Finally, although there are only a limited number of academic institutions that currently have the capacity to be a Type III regional interdisciplinary sleep program, this should not delay the establishment of the research network. Initially the network could consist of a limited number of programs. The network would benefit greatly from cultural, ethnic, and environmental diversity. Therefore, a long-range goal should be to have 8 to 10 geographically distributed Type III regional interdisciplinary sleep programs. In this report the committee does not recommend any research priorities. It is the committee's belief that the strategies outlined in the report will generate the appropriate mechanisms for generating a research agenda for the future of somnology and sleep medicine.

TABLE S-1 Guidelines for Interdisciplinary Type I, II, and III Academic Sleep Programs

Attribute	Type I (clinical)	Type II (clinical, training, research)	Type III (regionalized comprehensive centers)
Structure and Composition			
Clinical specialties represented: ^a			
Internal medicine and relevant subspecialties	x	x	x
Neurology	x	x	x
Psychiatry and subspecialties	x	x	x
Otolaryngology	x	x	x
Pediatrics and subspecialties (as necessary may be separate program)	x	x	x
Nursing	x	x	x
Psychology		x	x
Dentistry			x
Medical director certification in sleep medicine (American Board of Medical Specialties or American Board of Sleep Medicine) ^b	x	x	x
Consultant services from specialties not represented	x	x	x
Sleep specialists provide consultant services	x	x	x
Single accredited clinical sleep center	x	x	x
Comprehensive program for diagnosis and treatment of individuals	x	x	x

continued

TABLE S-1 continued

Attribute	Type I (clinical)	Type II (clinical, training, research)	Type III (regionalized comprehensive centers)
Training Program			
Training program for health care professionals and/or researchers	x	x	x
Medical school training and education	x	x	x
Education for residents in primary care	x	x	x
Residents in neurology, psychiatry, otolaryngology, and fellows in pulmonary medicine rotate through sleep program		x	x
Accredited fellowship program for physicians		x	x
Research training for clinical fellows		x	x
NIH-sponsored training grants for graduate and postgraduate researchers		x	x
Research Program			
Research areas of emphasis: ^c			
Neuroscience		x	x
Epidemiology/public health		x	x
Pharmacology			x
Basic or clinical research program		x	
Basic and clinical research program			x
Member of proposed national somnology and sleep medicine research and clinical network	x ^d	x	x
Regional coordinator for:			
Core facilities for basic research			x
Multisite clinical trials			x
Core facilities for clinical research			x
Mentoring of sleep fellows			x
Public education			x
Data coordinating site			x

^aThis list is not meant to be exclusive or exhaustive and should be modified as relevant specialties and training programs emerge.

^bCurrently this is American Board of Sleep Medicine. It is anticipated that in 2007 the examination would be supplanted by the American Board of Medical Specialties.

^cThis list is not meant to be exclusive or exhaustive. Other research areas could be involved (e.g., genetics, systems neurobiology, and bioengineering).

^dType I programs would be responsible for generating and submitting data to the national data registry established by the proposed National Somnology and Sleep Medicine Research and Clinical Network.

BOX S-1

Summary of Committee's Recommendations to Address and Remedy the Unmet Public Health Need

The following is a summary of the committee's recommendations. Complete text of each recommendation can be found in the corresponding chapters.

NATIONAL INSTITUTES OF HEALTH LEADERSHIP IN RESEARCH AND TRAINING

The National Center on Sleep Disorders Research and its advisory board should play a more proactive role in stimulating and coordinating the field. (Recommendation 8.1)

The National Institutes of Health and private foundations must increase investment in interdisciplinary somnology and sleep medicine research training and mentoring activities. (Recommendation 7.1)

The National Institutes of Health should ascertain the need for a transdisciplinary sleep laboratory that would serve as a core resource in its intramural clinical research program. (Recommendation 8.3)

PUBLIC AND PROFESSIONAL AWARENESS

The National Center on Sleep Disorders Research and the Centers for Disease Control and Prevention should establish a multi-media public education campaign. (Recommendation 5.1)

Academic health centers should integrate the teaching of somnology and sleep medicine into baccalaureate and doctoral health sciences programs, as well as residency and fellowship training and continuing professional development programs. (Recommendation 5.2)

SURVIELLANCE AND MONITORING

The Centers for Disease Control and Prevention and National Center on Sleep Disorders Research should support additional surveillance and monitoring of sleep patterns and sleep disorders. (Recommendation 5.3)

continued

BOX S-1 continued

TECHNOLOGY DEVELOPMENT

The National Institutes of Health and the Agency for Healthcare Research and Quality should support the validation and development of existing and new diagnostic and therapeutic technologies. (Recommendation 6.1)

INTERDISCIPLINARY SLEEP PROGRAMS IN ACADEMIC HEALTH CENTERS

New and existing sleep programs in academic health centers should conform to meet the criteria of a type I, II, or III interdisciplinary sleep program. (Recommendation 9.1)

Type I clinical interdisciplinary sleep program

Type II clinical, research, and training interdisciplinary sleep program

Type III regional comprehensive sleep program

It is recommended that the National Institutes of Health establish a national somnology and sleep medicine research network. (Recommendation 8.2)

Sleep laboratories should be part of accredited sleep centers, which include long-term strategies for patient care and chronic disease management. (Recommendation 9.2)

NOTE: For ease of reference, the committee's recommendations are numbered according to the chapter of the main text in which they appear followed by the order in which they appear in the chapter.

1

Introduction

*“Sleep that knits up the ravelled sleeve of care,
The death of each day’s life, sore labour’s bath,
Balm of hurt minds, great Nature’s
second course, Chief nourisher in life’s feast.”*
Shakespeare, *Macbeth*

CHAPTER SUMMARY *The public health burden of chronic sleep loss and sleep disorders is immense. Although clinical activities and scientific opportunities in the field are expanding, awareness among the general public and health care professionals is low, given the burden. The available workforce of health care providers is not sufficient to diagnose and treat individuals with sleep disorders. Therefore, the current situation necessitates a larger and more interdisciplinary workforce to meet health care demands as well as advance the field’s knowledge base. Further, there is a need to develop and reorganize public health and academic sleep programs to facilitate and improve the efficiency and effectiveness in public awareness, training, research, diagnosis, and treatment of sleep loss and sleep disorders. Finally, the fragmentation of research and clinical care currently present in most academic institutions requires the creation of accredited interdisciplinary sleep programs in academic institutions. The success of existing comprehensive academic Somnology and Sleep Medicine Programs offers evidence of the value of interdisciplinary approaches to patient care, education, research training, faculty development, and science. An interdisciplinary approach requires the coordinated and integrated effort of not only the major medical fields involved in sleep clinical care (internal medicine and its relevant subspecialties, pediatrics, neurology, psychiatry, psychology, and otolaryngology) but also other disciplines such as neuroscience, dentistry, nursing, and pharmacology.*

MAGNITUDE AND COST OF THE PROBLEM

Fatigued sleep, restless nights, hitting the alarm clock button for an additional 10 minutes of sleep—all are all too familiar manifestations of the interactions of life with one of the frontiers of science and clinical practice—somnology¹ and sleep medicine. It is estimated that 50 to 70 million Americans suffer from a chronic disorder of sleep and wakefulness (NHLBI, 2003), hindering daily functioning and adversely affecting health. The current capacity of America's health system is not sufficient to diagnose and treat all individuals with sleep disorders. Further, awareness among health care professionals and the general public is low considering the size of the problem. Among those individuals with sleep disorders are 3 to 4 million individuals with moderate to severe obstructive sleep apnea (Young et al., 1993), a disorder characterized by brief periods of recurrent cessation of breathing caused by airway obstruction with morbid or fatal consequences. Chronic insomnia, which hampers a person's ability to fall asleep, is observed in approximately 10 percent of the American population (Ford and Kamerow, 1989; Simon and VonKorff, 1997; Roth and Ancoli-Israel, 1999). Restless legs syndrome and periodic limb movement disorder are neurological conditions characterized by nocturnal limb movements and an irresistible urge to move the legs. These conditions affect approximately 5 percent of the general population (Lavigne and Montplaisir, 1994; Rothdach et al., 2000; NSF, 2000; Montplaisir et al., 2005), making it one of the most common movement disorders (Montplaisir et al., 2005).

The negative public health consequences of sleep loss and sleep-related disorders are enormous. Some of the most devastating human and environmental health disasters have been partially attributed to fatigue-related performance failures,² sleep loss, and night shift work-related performance failures, including the tragedy at the Union Carbide chemical plant in Bhopal, India; the nuclear reactor meltdowns at Three Mile Island and Chernobyl; and the grounding of the Exxon *Valdez* oil tanker (NCSDR, 1994; Moss and Sills, 1981; United States Senate Committee on Energy and National Resources, 1986; USNRC, 1987; Dinges et al., 1989). Each of these incidents not only cost millions of dollars but also had a disastrous impact on the environment and the health of local communities.

¹Somnology is the branch of science devoted to the study of the physiology of sleep, the behavioral dimensions of sleep, and the consequences of sleep loss and sleep disorders on an individual's and the general population's health, performance, safety, and quality of life. Sleep medicine is the branch of clinical medicine devoted to the diagnosis and treatment of individuals suffering from chronic sleep loss or sleep disorders.

²A significant portion of fatigue, but not all, is caused by chronic sleep loss and/or sleep disorders.

Over the past century, the average amount of time that Americans sleep has decreased by around 20 percent (NCSDR, 1994). Further, 1 out of every 5 workers in industrialized countries (well over 20 million Americans [OTA, 1991]) perform shift-work, which requires them to work at night and attempt to sleep during the daytime hours (AASM, 2005). These reversed sleep patterns cause maladjustment of circadian rhythms that often lead to sleep disruption. Americans are working more hours or multiple jobs and spending more time watching television and using the Internet, resulting in later sleep times and less sleep.

The cumulative long-term effects of sleep loss and sleep disorders have been associated with a wide range of deleterious health consequences, including an increased risk of hypertension, diabetes, obesity, heart attack, and stroke. In addition, sleep loss and sleep disorders have a significant economic impact. Billions of dollars a year are spent on direct medical costs associated with doctor visits, hospital services, prescriptions, and over-the-counter medications (NCSDR, 1994). Compared to healthy individuals, individuals with chronic sleep loss are less productive, have health care needs greater than the norm, and have an increased likelihood of injury; for example, it is estimated that there are 110,000 sleep-related injuries and 5,000 fatalities each year in motor vehicle crashes involving commercial trucks (CNTS, 1996).

HISTORICAL BACKGROUND

For centuries, sleep and dreams have long been topics of immense interest; however, the modern scientific study of sleep began relatively recently. In 1937 an electroencephalograph was used for the first time to observe the electrical activity in the brain during nonrapid eye movement sleep (Loomis et al., 1937). This opened the field to further advances. Rapid eye movement (REM) was discovered in 1953 by Kleitman and colleagues, and its correlation with dreams was a major step forward in understanding sleep physiology (Aserinsky and Kleitman, 1953). The culmination of this work came in 1957 when Dement and Kleitman defined the stages of sleep (see Chapter 2 of this report) (Dement and Kleitman, 1957). Since the 1950s a convergence of findings from many fields (e.g., neurology, pulmonology, neuroscience, psychiatry, otolaryngology, anatomy, and physiology) have led to a greater understanding of sleep as a basic universal biological process that affects the functioning of many organ systems (Shepard et al., 2005). In 1989, a seminal study demonstrated that rats that were subjected to total sleep deprivation developed skin lesions, experienced weight loss in spite of increased food intake, developed bacterial infections, and died within 2 to 3 weeks (Rechtschaffen et al., 1989). Researchers in sleep and circadian biology continue to work toward a greater understanding of the

etiology and pathophysiology of sleep disorders. The field is maturing into an interdisciplinary field in which integration and coordination across the traditional medical specialties, other health care providers (e.g. nurses, dentists), and between basic and clinical science is vital.

GROWTH OF SOMNOLOGY AND SLEEP MEDICINE

The maturation of the study of sleep and the field of Somnology and Sleep Medicine (Box 1-1) has seen the establishment of many organizations devoted to promoting public awareness, ensuring quality care for individuals who suffer from chronic sleep loss and sleep disorders, and supporting education and research endeavors. In addition to the National Center on Sleep Disorders Research (NCSDR) at the National Institutes of Health (NIH), professional societies and foundations have been established, including the American Academy of Sleep Medicine, the Sleep Research Society, the American Sleep Apnea Association, the Restless Legs Syndrome Foundation, and the National Sleep Foundation

The field of somnology and sleep medicine has been marked by a number of milestones over the last 35 years. Sleep laboratories dedicated to the evaluation and management of sleep disorders have been established. In 1970, sleep disorders were evaluated at only a handful of sleep laboratories in the world. In 2001, there were close to 1,300 sleep laboratories in the United States (Tachibana et al., 2005). Membership in the American Academy of Sleep Medicine and the Sleep Research Society and participation at the annual meeting of the American Professional Sleep Societies has continued to increase. In 2005 sleep medicine was recognized as a medical subspecialty by the Accreditation Council for Graduate Medical Education and the American Board of Medical Specialties.

CHALLENGES IN ADVANCING THE STUDY OF SLEEP DISORDERS

Coordinating Research and Research Funding

Integrating and coordinating the efforts of the many relevant institutes and centers at the NIH presents many challenges related to funding and advancing somnology research. For example, it has recently been recognized that restless legs syndrome (National Institute of Neurological Disorders and Stroke) and sleep apnea (National Heart, Lung, and Blood Institute) may be a major cause of attention deficit hyperactivity disorder (National Institute of Child Health and Human Development, National Institute of Mental Health) and other behavioral problems (Chervin et al., 2002). The National Institute on Aging is interested in the increase in sleep

BOX 1-1 Defining Somnology and Sleep Medicine

Throughout information gathering workshops and discussions the Committee on Sleep Medicine and Research heard the field and practice of somnology and sleep medicine referred to in many different terms: *sleep*, *sleep medicine*, *sleep disorders research*, *sleep research and medicine*, and the *study of sleep*. These terms and others fail to describe the full extent of the study and practice of somnology and sleep medicine. In response to this and the emergence of the clinical and research field, this committee believes that an enhanced vocabulary would be helpful to describe the study of sleep and circadian rhythms. Therefore, throughout this report the committee will use the terms *somnology* and *sleep medicine*.

Somnology: Somnology is the branch of science devoted to the study of the physiology of sleep, the behavioral dimensions of sleep, and the consequences of sleep loss and sleep disorders on an individual's and the general population's health, performance, safety, and quality of life.

Sleep medicine: Sleep medicine is a branch of clinical medicine devoted to the diagnosis and treatment of individuals suffering from chronic sleep loss or sleep disorders.

and wake disruption during senescence. Insomnia is typically treated using behavioral therapy techniques (Office of Behavioral and Social Sciences Research) and is often comorbid with depression, eating disorders, and other mental disorders (National Institute of Mental Health). Drugs of abuse, including alcohol and stimulants (National Institute on Drug Abuse, National Institute on Alcohol Abuse and Alcoholism), have major effects on sleep and are often used to treat underlying sleep problems such as insomnia or narcolepsy. Sleep apnea research and therapy cuts across a number of disciplines, including nursing (National Institute of Nursing Research), dentistry and otolaryngology (National Institute of Dental and Craniofacial Research), surgery, neurology (National Institute of Neurological Disorders and Stroke), cardiology, and pulmonary medicine (National Heart, Lung, and Blood Institute). At the basic research level, somnology research often involves multiple disciplines such as genetics (National Human Genome Research Institute), environmental sciences (National Institute of Environmental Health Sciences), epidemiology, immunology (National Institute of Allergy and Infectious Diseases), endocrinology (National Institute of Diabetes and Digestive and Kidney Diseases), neurosciences (National

Institute of Neurological Disorders and Stroke, National Institute of Mental Health, National Eye Institute), and otolaryngology (National Institute on Deafness and Other Communication Disorders).

Trans-NIH Sleep Research Coordinating Committee

To facilitate an interchange of information on somnology research the Trans-NIH Sleep Research Coordinating Committee was formed in 1986. The coordinating committee consists of representatives from 13 NIH institutes and centers and meets quarterly to discuss current sleep-related activities in the NIH and to develop new programs.

National Center on Sleep Disorders Research

In 1993 the National Heart, Lung, and Blood Institute established the NCSDR. As described in the congressional language, the mission of the NCSDR is the “conduct and support of biomedical and related research and research training, the dissemination of health information, and the conduct of other programs with respect to various sleep disorders, the basic understanding of sleep, biological and circadian rhythm research, chronobiology, and other sleep related research”³ (see Appendix D).

The function of the NCSDR and the Trans-NIH Sleep Research Coordinating Committee are intertwined. The director of the NCSDR serves as Chair of the Coordinating Committee. Further, the NCSDR is responsible for coordinating the information collected by individual institutions for the Coordinating Committee’s annual report; including sleep related activities, initiatives, and funding of sleep-related activities.

NIH funding for somnology research has increased by more than 150 percent since the NCSDR became fully operational in 1996, reaching a total of \$196.2 million (0.07 percent of the NIH budget) in fiscal year 2004 (NHLBI, 2003). However, this growth occurred during the same period that the overall budget to the NIH doubled, and currently NIH funding for sleep-related activities is reaching a plateau. In 2004, for the first time since the NCSDR was established, there was a decrease in annual NIH expenditures for sleep-related projects; there were fewer research project grants funded in 2004, and the number of new grants awarded also decreased (see Appendix G). Consequently, the future outlook for somnology and sleep medicine is unclear. This presents an even greater challenge for a field that requires growth in its scientific workforce and technology.

³National Institutes of Health Revitalization Act of 1993. Pub. L. No. 103-43 (1993).

Increasing the Numbers of Trained Researchers and Clinicians

New investigators and clinicians knowledgeable about sleep-related research and clinical care are needed. The growth of the discipline in terms of clinical volume has not been reflected in a corresponding increase in the number of clinical and basic sleep researchers. In the spring of 2005 there were 781 American members of the Sleep Research Society, a number representing the majority of individuals performing sleep-related research. There are only 253 principal investigators who work on sleep-related research. There are 151 researchers involved primarily in clinical sleep research, and 126 focus primarily on basic research projects. In 2004, of the top 30 academic institutions that received the greatest number of grants from the NIH, less than half had career development and training awards in somnology and sleep medicine, and only 17 had NIH-sponsored fellowships that were sleep related. Between the years 2000 and 2004, the NIH increased its support of sleep-related training and fellowship grants; however, during this same period there was a decrease in the number of career development awards. Over the same period, the number of academic institutions receiving sleep-related career development awards also decreased. Therefore, creating an infrastructure to develop a workforce capable of meeting the clinical and scientific demand remains a major challenge.

Time devoted in medical school curriculum to sleep medicine is limited. The percentage of medical schools that include sleep disorders in their curriculums has risen modestly from 54 percent in 1978 (Orr et al., 1980) to 63 percent in 1993, but the time devoted averages only 2.11 hours (Rosen et al., 1998). Similar analysis has not recently been performed, but there is no evidence to suggest that medical schools are placing increased emphasis on sleep-related content in their curriculums. Clearly, the educational effort is still inadequate given the magnitude of the morbid effects that sleep loss and sleep disorders have on the most common diseases (e.g., obesity, hypertension, heart attack, and diabetes). In response to this perceived shortcoming in sleep education, the National Heart, Lung, and Blood Institute supported a series of grants (K07 funding mechanism) to develop model medical school curricula. This resulted in the establishment of MEDSleep, a collection of over 75 sleep education tools and products (AASM, 2005). Although this program generated a large number of resources, it is unclear how many of them have been used and implemented. Despite these advances, physician education regarding the recognition, diagnosis, management, and treatment of sleep disorders is still inadequate (Strohl et al., 2003; Owens, 2005).

To strengthen the interdisciplinary aspects of the field it is important to attract new investigators to the field and expand the number of trained somnology scientists in other relevant and related disciplines. These areas

include, but are not limited to, biology and health informatics, health service research, nursing, epidemiology and genetic epidemiology, clinical trials, functional imaging, genetics, pathology, neurosciences, and molecular biology.

Distribution of Resources and Technology Development

Today, the capacity needed to serve the population seeking diagnosis and treatment is inadequate. Analysis commissioned on behalf of the committee indicated that in many health care systems and communities, the waiting time for a polysomnogram, the procedure used to diagnose many sleep disorders, may be as much as 10 weeks (see Chapter 9). This shortfall will worsen as awareness of the clinical consequences and public health burden of sleep disorders increases. A substantial investment is needed to enlarge the clinical and research workforce and improve the technology for diagnosis and treatment. Ambulatory diagnostic technologies currently available need to be validated. Further, there is a need for improved treatments for individuals with chronic sleep loss and sleep disorders. For example, the most common treatment for sleep apnea, continuous positive airway pressure therapy, which requires an individual to wear a mask over the face while sleeping, has a low rate of compliance, between 45 to 70 percent (Kribbs et al., 1993).

There are approximately 1,300 sleep laboratories in the United States, 39 percent of which are accredited by the American Academy of Sleep Medicine (Tachibana et al., 2005). However, millions of individuals suffering from sleep disorders remain undiagnosed and untreated (Young et al., 1997; Kapur et al., 2002). The utilization and capacity of sleep laboratories is not distributed based on the prevalence of sleep disorders (Tachibana et al., 2005). Apart from creating new sleep centers and laboratories, developing and validating reliable portable diagnostic technologies is required to meet the demand that will arise from greater awareness among the general public (see Chapter 6).

SOMNOLOGY AND SLEEP MEDICINE RESEARCH IN ACADEMIC INSTITUTIONS

The division of a university and medical school into academic departments is based upon distinct clinical and graduate training programs. Many of the most promising new lines of academic research and the most effective clinical services depend on strong, interdisciplinary programs that emerge from the knowledge base of the more traditional disciplines (CFAT, 2001). Unfortunately, the organization of academic disciplines among the schools and colleges does not effectively support existing interdisciplinary programs

or those that could be created (Ehrenberg and Epifantseva, 2001; Thursby and Thursby, 2002).

Somnology and Sleep Medicine Is an Interdisciplinary Field

The field of Somnology and Sleep Medicine is an emerging interdisciplinary field that is being forged from several existing sciences and medical specialties. However, the current organization of academic health centers houses clinicians and scientists in discrete departments that do not favor interdisciplinary research efforts. Although the scientific enterprise of the field requires interdisciplinary strategies, the clinical service of patients is multidisciplinary and requires linkages to other medical specialties.

As described in the National Academy of Sciences (2004) report *Facilitating Interdisciplinary Research*:

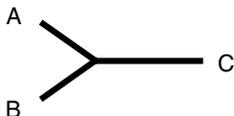
Interdisciplinary research is a mode of research performed by teams or individuals that integrates information, data, techniques, tools, perspectives, concepts, and/or theories from two or more disciplines or bodies of specialized knowledge to advance fundamental understanding or to solve problems whose solutions are beyond the scope of a single discipline or field of research practice (Figure 1-1A).

Multidisciplinary research is taken to mean research that involves more than a single discipline in which each discipline makes a separate contribution. Investigators may share facilities and research approaches while working separately on distinct aspects of a problem (Figure 1-1B) (NAS, 2004).

There are a wide range of programs in Somnology and Sleep Medicine. Some are solely clinical in nature; others are clinical programs that include training of physicians and some research. There are also a limited number of comprehensive programs that emphasize clinical care education and training, as well as basic and clinical research. With few exceptions most programs continue to be not integrated and embedded in medical departments. This organization has many adverse implications for the field; including:

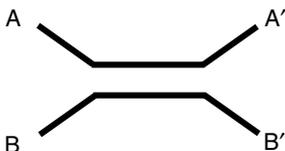
- Clinical training in sleep loss and sleep disorders is often limited to those in the department where the program is housed to the exclusion of others.
 - The absence of interdisciplinary clinical teams hinders patient care.
 - A limited sense of identity with, or focus on the field, and an absence of an established career path for faculty makes it difficult to attract new students, researchers, and clinicians into the field.

A) Interdisciplinary



Joined together to work on a common question or problem. Interaction may forge a new research field or discipline.

B) Multidisciplinary



Disciplines joined together to work on a common question or problem, split apart when work is complete, having likely gained new knowledge, insight, strategies from other disciplines.

FIGURE 1-1 Interdisciplinary and multidisciplinary research.

SOURCE: National Academy of Sciences, 2004.

- Research or clinical funds generated from sleep-related activities are not generally reinvested to enhance sleep programs.
- Collaboration can be more difficult because researchers and clinicians are geographically dispersed.

Sleep Loss and Sleep Disorders Require Long-Term Patient Care and Chronic Disease Management

Sleep disorders are chronic conditions necessitating complex treatments. They are frequently comorbid with other sleep disorders and other conditions (e.g., cardiovascular disease, depression, or diabetes), which, by themselves, are complex to treat. Despite the importance of early recognition and treatment, the primary focus of most existing sleep centers is on diagnosis, rather than on comprehensive care of sleep loss and sleep disorders as chronic conditions. The narrow focus of sleep centers may largely be the unintended result of accreditation criteria, which emphasize diagnostic standards and reimbursement for the diagnostic testing (see Chapter 9).

SCOPE AND ORGANIZATION OF THIS REPORT

Increased public education and greater awareness of the burden of sleep loss and sleep disorders as well as scientific advances have poised the field of somnology and sleep medicine for great strides. In 2003 the NCSDR published a set of research priorities for the field. However, advances will require an organized strategy to increase and coordinate efforts in training and educating the public, researchers, and clinicians, as well as improved infrastructure and funding for this endeavor.

Recognizing the need to develop a new coordinated strategy to improve public awareness and strengthen the field of Somnology and Sleep Medicine, the NCSDR at the NIH, along with the American Academy of Sleep Medicine, the National Sleep Foundation, and the Sleep Research Society, requested that the Institute of Medicine (IOM) conduct a study that would examine: (1) the public health significance of sleep, sleep loss, and sleep disorders, (2) gaps in the public health system and adequacy of the current resources and infrastructures for addressing the gaps, (3) barriers and opportunities for improving interdisciplinary research and medical education and training in the area of sleep and sleep medicine, and (4) develop a comprehensive plan for enhancing sleep medicine and sleep research (Box 1-2).

The IOM appointed a 14-member committee with expertise in academic and medical administration, adolescent medicine, cardiology, epidemiology, geriatrics, health sciences research, neurology, nursing, otolaryngology, pediatrics, psychiatry, and pulmonology. The committee met five times during the course of its work and held two workshops that provided input on the current public health burden of sleep loss and chronic sleep disorders and the organization and operation of various types of academic sleep programs.

Chapter 2 of this report describes the basic biology and physiology of sleep and circadian rhythms. Chapter 3 introduces the primary sleep disorders and their associated health burdens, and Chapter 4 describes their impact on an individual's performance and associated economic impact. Chapter 5 provides an overview of the barriers to providing optimal patient care, including the lack of public and professional education. Chapter 6 highlights the need for greater capacity to diagnose and treat individuals with sleep loss and sleep disorders. In Chapter 7, the committee examines the education and training programs for students, scientists, and health care professionals. Chapter 8 discusses the current investment by the NIH and the NCSDR and the potential role of a national somnology and sleep medicine research network for advancing therapeutic interventions for sleep loss and sleep disorders. Chapter 9 highlights the infrastructure of the field and proposes recommendations for developing academic programs in somnology and sleep medicine.

BOX 1-2
Statement of Task

The Institute of Medicine will convene an ad hoc committee of experts in public health, academic and medical administration, and health sciences research to identify (1) the public health significance of sleep, sleep loss, and sleep disorders; (2) barriers and opportunities for improving interdisciplinary research and medical education and training in the area of sleep and sleep medicine; and (3) strategies for developing increased support for sleep medicine and sleep research in academic health centers.

The committee will:

1. Review and quantify the public health significance of sleep health, sleep loss, and sleep disorders based on current knowledge. This task will include assessments of (a) the contribution of sleep disorders to poor health, reduced quality of life, and early mortality; and (b) the economic consequences of sleep loss and sleep disorders, including lost wages and productivity. Target populations will be segmented as children, adults, and the elderly.
2. Identify gaps in the public health system relating to the understanding, management, and treatment of sleep loss and sleep disorders, and assess the adequacy of the current resources and infrastructures for addressing the gaps. The committee, however, will not be responsible for making any budgetary recommendations.
3. Identify barriers to and opportunities for improving and stimulating multidisciplinary research, education, and training in sleep medicine. Delineate fiscal and academic organizational models that promote and facilitate (a) sleep research in the basic sciences; (b) cooperative research efforts between basic science disciplines and clinical practice specialties; and (c) multidisciplinary efforts in education and training of practitioners in sleep health, sleep disorders, and sleep research.
4. Develop a comprehensive plan for enhancing sleep medicine and sleep research, as appropriate, for improving the public's health. This will include interdisciplinary initiatives for research, medical education, training, clinical practice, and health policy.

REFERENCES

- AASM (American Academy of Sleep Medicine). 2005. *MedSleep*. [Online]. Available: http://www.aasmnet.org/MedSleep_Home.aspx [accessed December 17, 2005].
- Aserinsky E, Kleitman N. 1953. Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science* 118(3062):273–274.
- CFAT (Carnegie Foundation for the Advancement of Teaching). 2001. *The Carnegie Classification of Institutions of Higher Education*. Princeton, NJ: Carnegie Foundation for the Advancement of Teaching.
- Chervin RD, Hedger Archbold K, Dillon JE, Pituch KJ, Panahi P, Dahl RE, Guilleminault C. 2002. Associations between symptoms of inattention, hyperactivity, restless legs, and periodic leg movements. *Sleep* 25(2):213–218.
- CNTS (Center for National Truck Statistics). 1996. *Truck and Bus Accident Factbook—1994*. UMTRI-96-40. Washington, DC: Federal Highway Administration Office of Motor Carriers.
- Dement W, Kleitman N. 1957. Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. *Electroencephalography and Clinical Neurophysiology Supplement* 9(4):673–690.
- Dinges DF, Graeber RC, Carskadon MA, Czeisler CA, Dement WC. 1989. Attending to inattention. *Science* 245(4916):342.
- Ehrenberg RG, Epifantseva J. 2001. Has the growth of science crowded out other things at universities? *Change* 26:46–52.
- Ford DE, Kamerow DB. 1989. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *Journal of the American Medical Association* 262(11):1479–1484.
- Kapur V, Strohl KP, Redline S, Iber C, O'Connor G, Nieto J. 2002. Underdiagnosis of sleep apnea syndrome in U.S. communities. *Sleep and Breathing* 6(2):49–54.
- Kribbs NB, Pack AI, Kline LR, Smith PL, Schwartz AR, Schubert NM, Redline S, Henry JN, Getsy JE, Dinges DF. 1993. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *American Review of Respiratory Disease* 147(4):887–895.
- Lavigne GJ, Montplaisir JY. 1994. Restless legs syndrome and sleep bruxism: Prevalence and association among Canadians. *Sleep* 17(8):739–743.
- Loomis AL, Harvey EN, Hobart GA. 1937. Cerebral states during sleep as studied by human brain potentials. *Journal of Experimental Psychology* 21:127–144.
- Montplaisir J, Allen RP, Walters AD, Lerini-Strambi L. 2005. Restless legs syndrome and periodic limb movements during sleep. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 839–852.
- Moss TH, Sills DL, 1981. *The Three Mile Island Nuclear Accident: Lessons and Implications*. New York: New York Academy of Sciences.
- NAS (National Academy of Sciences). 2004. *Facilitating Interdisciplinary Research*. Washington, DC: The National Academies Press.
- NCSDR (National Commission on Sleep Disorders Research). 1994. *Wake Up America: A National Sleep Alert. Volume II: Working Group Reports*. 331-355/30683. Washington, DC: Government Printing Office.
- NHLBI (National Heart, Lung, and Blood Institute). 2003. *National Sleep Disorders Research Plan, 2003*. Bethesda, MD: National Institutes of Health.

- NSF (National Sleep Foundation). 2000. *2000 Omnibus Sleep in America Poll*. [Online]. Available: <http://www.sleepfoundation.org/publications/2001poll.html> [accessed May 25, 2005].
- Orr WC, Stahl ML, Dement WC, Reddington D. 1980. Physician education in sleep disorders. *Journal of Medical Education* 55(4):367–369.
- OTA (Office of Technology Assessment). 1991. *Biological Rhythms: Implications for the worker*. OTA-BA-463. Washington, DC: Government Printing Office.
- Owens J. 2005. Introduction to special section: NIH Sleep Academic Award program. *Sleep Medicine* 6(1):45–46.
- Rechtschaffen A, Bergmann BM, Everson CA, Kushida CA, Gilliland MA. 1989. Sleep deprivation in the rat: X. Integration and discussion of the findings. *Sleep* 12(1):68–87.
- Rosen R, Mahowald M, Chesson A, Doghramji K, Goldberg R, Moline M, Millman R, Zammit G, Mark B, Dement W. 1998. The Taskforce 2000 Survey on Medical Education in Sleep and Sleep Disorders. *Sleep* 21(3):235–238.
- Roth T, Ancoli-Israel S. 1999. Daytime consequences and correlates of insomnia in the United States: Results of the 1991 National Sleep Foundation survey. II. *Sleep* 22(suppl 2):S354–S358.
- Rothdach AJ, Trenkwalder C, Haberstocck J, Keil U, Berger K. 2000. Prevalence and risk factors of RLS in an elderly population: The MEMO study. Memory and morbidity in Augsburg elderly. *Neurology* 54(5):1064–1068.
- Shepard JJW, Buysse DJ, Chesson JAL, Dement WC, Goldberg R, Guilleminault C, Harris CD, Iber C, Mignot E, Mitler MM, Moore KE, Phillips BA, Quan SF, Rosenberg RS, Roth T, Schmidt HS, Silber MS, Walsh JK, White DP. 2005. History of the development of sleep medicine in the United States. *Journal of Clinical Sleep Medicine* 1(1):61–82.
- Simon GE, VonKorff M. 1997. Prevalence, burden, and treatment of insomnia in primary care. *American Journal of Psychiatry* 154(10):1417–1423.
- Strohl KP, Veasey S, Harding S, Skatrud J, Berger HA, Papp KK, Dunagan D, Guilleminault C. 2003. Competency-based goals for sleep and chronobiology in undergraduate medical education. *Sleep* 26(3):333–336.
- Tachibana N, Ayas TA, White DP. 2005. A quantitative assessment of sleep laboratory activity in the United States. *Journal of Clinical Sleep Medicine* 1(1):23–26.
- Thursby JG, Thursby TM. 2002. Who is selling the ivory tower? Sources of growth in university licensing. *Management Science* 48(1):90–104.
- United States Senate Committee on Energy and Natural Resources. 1986. *The Chernobyl Accident*. Washington, DC: Government Printing Office.
- USNRC (United States Nuclear Regulatory Commission). 1987. *Report on the Accident at the Chernobyl Nuclear Power Station*. NU-REG 1250. Washington, DC: Government Printing Office.
- Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. 1993. The occurrence of sleep-disordered breathing among middle-aged adults. *New England Journal of Medicine* 328(17):1230–1235.
- Young T, Evans L, Finn L, Palta M. 1997. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep* 20(9):705–706.

2

Sleep Physiology

CHAPTER SUMMARY *This chapter provides a brief overview of sleep physiology and how sleep patterns change over an individual's life span. Humans spend about one-third of their lives asleep. There are two types of sleep, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. NREM sleep is divided into stages 1, 2, 3, and 4, representing a continuum of relative depth. Each has unique characteristics including variations in brain wave patterns, eye movements, and muscle tone. Circadian rhythms, the daily rhythms in physiology and behavior, regulate the sleep-wake cycle. In addition, the sleep-wake system is thought to be regulated by the interplay of two major processes, one that promotes sleep and one that maintains wakefulness.*

Humans spend about one-third of their lives asleep, yet most individuals know little about sleep. Although its function remains to be fully elucidated, sleep is a universal need of all higher life forms including humans, absence of which has serious physiological consequences. This chapter provides an overview of basic sleep physiology and describes the characteristics of REM and NREM sleep. Sleep and circadian-generating systems are also reviewed. The chapter ends with a discussion about how sleep patterns change over an individual's life span.

SLEEP ARCHITECTURE

Sleep architecture refers to the basic structural organization of normal sleep. There are two types of sleep, non-rapid eye-movement (NREM) sleep and rapid eye-movement (REM) sleep. NREM sleep is divided into stages 1, 2, 3, and 4, representing a continuum of relative depth. Each has unique characteristics including variations in brain wave patterns, eye movements, and muscle tone. Sleep cycles and stages were uncovered with the use of electroencephalographic (EEG) recordings that trace the electrical patterns of brain activity (Loomis et al., 1937; Dement and Kleitman, 1957a).

Two Types of Sleep

Over the course of a period of sleep, NREM and REM sleep alternate cyclically (Figure 2-1). The function of alternations between these two types of sleep is not yet understood, but irregular cycling and/or absent sleep stages are associated with sleep disorders (Zepelin et al., 2005). For example, instead of entering sleep through NREM, as is typical, individuals

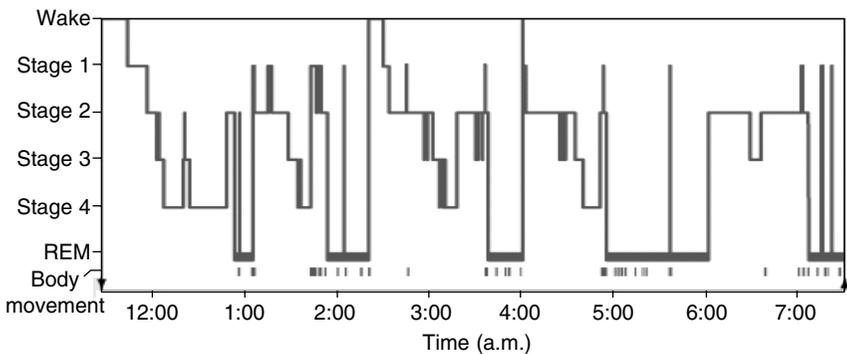


FIGURE 2-1 Progression of sleep states across a single night in young adult. SOURCE: Carskadon and Dement (2005).

with narcolepsy enter sleep directly into REM sleep (Carskadon and Rechtschaffen, 2005).

NREM and REM Sleep Cycles

A sleep episode begins with a short period of NREM stage 1 progressing through stage 2, followed by stages 3 and 4 and finally to REM. However, individuals do not remain in REM sleep the remainder of the night but, rather, cycle between stages of NREM and REM throughout the night (Figure 2-1). NREM sleep constitutes about 75 to 80 percent of total time spent in sleep, and REM sleep constitutes the remaining 20 to 25 percent. The average length of the first NREM-REM sleep cycle is 70 to 100 minutes. The second, and later, cycles are longer lasting—approximately 90 to 120 minutes (Carskadon and Dement, 2005). In normal adults, REM sleep increases as the night progresses and is longest in the last one-third of the sleep episode. As the sleep episode progresses, stage 2 begins to account for the majority of NREM sleep, and stages 3 and 4 may sometimes altogether disappear.

Four Stages of NREM Sleep

The four stages of NREM sleep are each associated with distinct brain activity and physiology. Figure 2-2 shows the EEG patterns characteristic of the four NREM stages. Other instruments are used to track characteristic changes in eye movement and muscle tone.

Stage 1 Sleep

NREM stage 1 sleep serves a transitional role in sleep-stage cycling. Aside from newborns and those with narcolepsy and other specific neurological disorders, the average individual's sleep episode begins in NREM stage 1. This stage usually lasts 1 to 7 minutes in the initial cycle, constituting 2 to 5 percent of total sleep, and is easily interrupted by a disruptive noise. Brain activity on the EEG in stage 1 transitions from wakefulness (marked by rhythmic alpha waves) to low-voltage, mixed-frequency waves. Alpha waves are associated with a wakeful relaxation state and are characterized by a frequency of 8 to 13 cycles per second (Carskadon and Dement, 2005).

Stage 2 Sleep

Stage 2 sleep lasts approximately 10 to 25 minutes in the initial cycle and lengthens with each successive cycle, eventually constituting between 45 to 55 percent of the total sleep episode. An individual in stage 2 sleep

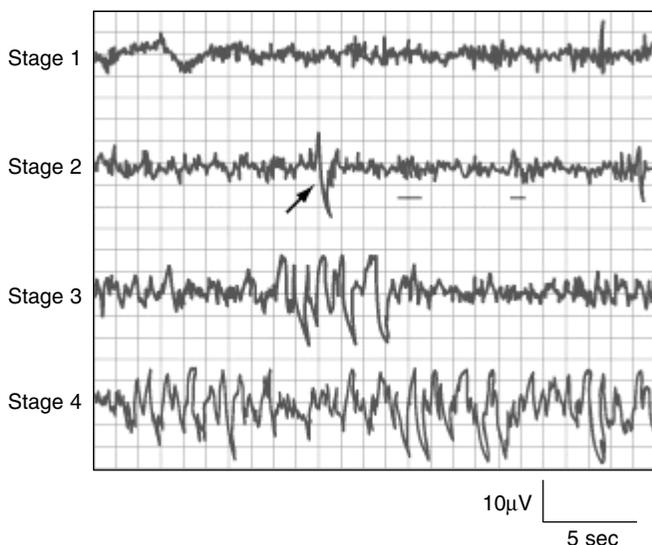


FIGURE 2-2 Characteristic EEG activity of each of the four stages of NREM sleep. NOTE: In stage 2, the arrow indicates a K-complex, and the underlining shows two sleep spindles.

SOURCE: Carskadon and Dement (2005).

requires more intense stimuli than in stage 1 to awaken. Brain activity on an EEG shows relatively low-voltage, mixed-frequency activity characterized by the presence of sleep spindles and K-complexes (Figure 2-2). It is hypothesized that sleep spindles are important for memory consolidation. Individuals who learn a new task have a significantly higher density of sleep spindles than those in a control group (Gais et al., 2002).

Stages 3 and 4, Slow-Wave Sleep

Sleep stages 3 and 4 are collectively referred to as slow-wave sleep (SWS), most of which occurs during the first third of the night. Each has distinguishing characteristics. Stage 3 lasts only a few minutes and constitutes about 3 to 8 percent of sleep. The EEG shows increased high-voltage, slow-wave activity (Figure 2-2).

The last NREM stage is stage 4, which lasts approximately 20 to 40 minutes in the first cycle and makes up about 10 to 15 percent of sleep. The arousal threshold is highest for all NREM stages in stage 4. This stage is

characterized by increased amounts of high-voltage, slow-wave activity on the EEG (Carskadon and Dement, 2005).

REM Sleep

REM sleep is defined by the presence of desynchronized (low-voltage, mixed-frequency) brain wave activity, muscle atonia, and bursts of rapid eye movements (Carskadon and Dement, 2005). “Sawtooth” wave forms, theta activity (3 to 7 counts per second), and slow alpha activity also characterize REM sleep. During the initial cycle, the REM period may last only 1 to 5 minutes; however, it becomes progressively prolonged as the sleep episode progresses (Carskadon and Dement, 2005). There are numerous physiological differences between NREM and REM sleep (Table 2-1).

TABLE 2-1 Physiological Changes During NREM and REM Sleep

Physiological Process	NREM	REM
Brain activity	Decreases from wakefulness	Increases in motor and sensory areas, while other areas are similar to NREM
Heart rate	Slows from wakefulness	Increases and varies compared to NREM
Blood pressure	Decreases from wakefulness	Increases (up to 30 percent) and varies from NREM
Sympathetic nerve activity	Decreases from wakefulness	Increases significantly from wakefulness
Muscle tone	Similar to wakefulness	Absent
Blood flow to brain	Decreases from wakefulness	Increases from NREM, depending on brain region
Respiration	Decreases from wakefulness	Increases and varies from NREM, but may show brief stoppages; coughing suppressed
Airway resistance	Increases from wakefulness	Increases and varies from wakefulness
Body temperature	Is regulated at lower set point than wakefulness; shivering initiated at lower temperature than during wakefulness	Is not regulated; no shivering or sweating; temperature drifts toward that of the local environment
Sexual arousal	Occurs infrequently	Greater than NREM

SOURCES: NHLBI (2003), Somers et al. (1993), Madsen et al. (1991b).

Dreaming is most often associated with REM sleep. Loss of muscle tone and reflexes likely serves an important function because it prevents an individual from “acting out” their dreams or nightmares while sleeping (see Chapter 3) (Bader et al., 2003). Approximately 80 percent of vivid dream recall results after arousal from this stage of sleep (Dement and Kleitman, 1957b). REM sleep may also be important for memory consolidation (Crick and Mitchison, 1983; Smith and Lapp, 1991).

Physiology During Sleep

In addition to the physiological changes listed in Table 2-1, there are other body system changes that occur during sleep. Generally, these changes are well tolerated in healthy individuals, but they may compromise the sometimes fragile balance of individuals with vulnerable systems, such as those with cardiovascular diseases (Parker and Dunbar, 2005). Physiological changes also occur in the following systems:

- **Cardiovascular:** Changes in blood pressure and heart rate occur during sleep and are primarily determined by autonomic nervous system activity. For instance, brief increases in blood pressure and heart rate occur with K-complexes, arousals, and large body movements (Lugaresi et al., 1978; Catcheside et al., 2002; Blasi et al., 2003; Tank et al., 2003). Further, there is an increased risk of myocardial infarction in the morning due to the sharp increases in heart rate and blood pressure that accompany awakening (Floras et al., 1978; Mulcahy et al., 1993).
- **Sympathetic-nerve activity:** Sympathetic-nerve activity decreases as NREM sleep deepens; however, there is a burst of sympathetic-nerve activity during NREM sleep due to the brief increase in blood pressure and heart rate that follows K-complexes. Compared to wakefulness, there is a rise in activity during REM sleep (Somers et al., 1993).
- **Respiratory:** Ventilation and respiratory flow change during sleep and become increasingly faster and more erratic, specifically during REM sleep (Krieger, 2000; Simon et al., 2002). Ventilation data during REM sleep are somewhat unclear, but they suggest that hypoventilation (deficient ventilation of the lungs that results in reduction in the oxygen content or increase in the carbon dioxide content of the blood or both) occurs in a similar way as during NREM sleep (NLM, 2006). Several factors contribute to hypoventilation during NREM, and possibly REM, sleep such as reduced pharyngeal muscle tone (Krieger, 2000; Simon et al., 2002). Further, during REM sleep, there is reduced rib cage movement and increased upper airway resistance due to the loss of tone in the intercostals and upper airway muscles (Parker and Dunbar, 2005). More generally, ventilation and respiratory flow show less effective adaptive responses dur-

ing sleep. The cough reflex, which normally reacts to irritants in the airway, is suppressed during REM and NREM sleep. The hypoxic ventilatory response is also lower in NREM sleep than during wakefulness and decreases further during REM sleep. Similarly, the arousal response to respiratory resistance (for example, resistance in breathing in or out) is lowest in stage 3 and stage 4 sleep (Douglas, 2005).

- **Cerebral blood flow:** NREM sleep is associated with significant reductions in blood flow and metabolism, while total blood flow and metabolism in REM sleep is comparable to wakefulness (Madsen et al., 1991b). However, metabolism and blood flow increase in certain brain regions during REM sleep, compared to wakefulness, such as the limbic system (which is involved with emotions), and visual association areas (Madsen et al., 1991a).

- **Renal:** There is a decreased excretion of sodium, potassium, chloride, and calcium during sleep that allows for more concentrated and reduced urine flow. The changes that occur during sleep in renal function are complex and include changes in renal blood flow, glomerular filtration, hormone secretion, and sympathetic neural stimulation (Cianci et al., 1991; Van Cauter, 2000; Buxton et al., 2002).

- **Endocrine:** Endocrine functions such as growth hormone, thyroid hormone, and melatonin secretion are influenced by sleep. Growth hormone secretion typically takes place during the first few hours after sleep onset and generally occurs during SWS, while thyroid hormone secretion takes place in the late evening. Melatonin, which induces sleepiness, likely by reducing an alerting effect from the suprachiasmatic nucleus, is influenced by the light-dark cycle and is suppressed by light (Parker and Dunbar, 2005).

SLEEP-WAKE REGULATION

The Two-Process Model

The sleep-wake system is thought to be regulated by the interplay of two major processes, one that promotes sleep (process S) and one that maintains wakefulness (process C) (Gillette and Abbott, 2005). Process S is the homeostatic drive for sleep. The need for sleep (process S) accumulates across the day, peaks just before bedtime at night and dissipates throughout the night.

Process C is wake promoting and is regulated by the circadian system. Process C builds across the day, serving to counteract process S and promote wakefulness and alertness. However, this wake-promoting system begins to decline at bedtime, serving to enhance sleep consolidation as the need for sleep dissipates across the night (Gillette and Abbott, 2005). With an adequate night's rest, the homeostatic drive for sleep is reduced, the

circadian waking drive begins to increase, and the cycle starts over. In the absence of process C, total sleep time remains the same, but it is randomly distributed over the day and night; therefore, process C also works to consolidate sleep and wake into fairly distinct episodes (Gillette and Abbott, 2005). Importantly, through synchronization of the circadian system, process C assists in keeping sleep-wakefulness cycles coordinated with environmental light-dark cycles.

Sleep-Generating Systems in the Brainstem

Sleep process S is regulated by neurons that shut down the arousal systems, thus allowing the brain to fall asleep. Many of these neurons are found in the preoptic area of the hypothalamus (Figure 2-3A). These neurons, containing molecules that inhibit neuronal communication, turn off the arousal systems during sleep. Loss of these nerve cells causes profound insomnia (Saper et al., 2005a,c). Inputs from other regions of the brain also greatly influence the sleep system. These include inputs from the lower brainstem that relay information about the state of the body (e.g., a full stomach is conducive to falling asleep), as well as from emotional and cognitive areas of the forebrain. In addition, as described further in the next section, there are inputs from the circadian system that allow the wake-sleep system to synchronize with the external day-night cycle, but also to override this cycle when it is necessitated by environmental needs.

The sleep-generating system also includes neurons in the pons that intermittently switch from NREM to REM sleep over the course of the night. These neurons send outputs to the lower brainstem and spinal cord that cause muscle atonia, REMs, and chaotic autonomic activity that characterize REM sleep. Other outputs are sent to the forebrain, including activation of the cholinergic pathways to the thalamus to activate the EEG.

Wake-Generating Systems in the Brainstem

Wakefulness is generated by an ascending arousal system from the brainstem that activates forebrain structures to maintain wakefulness (Figure 2-3B). This idea, originally put forward by Moruzzi and Magoun (1949), has more recently been refined (Jones, 2005a; Saper et al., 2005c). The main source for the ascending arousal influence includes two major pathways that originate in the upper brainstem. The first pathway, which takes origin from cholinergic neurons in the upper pons, activates parts of the thalamus that are responsible for maintaining transmission of sensory information to the cerebral cortex. The second pathway, which originates in cell groups in the upper brainstem that contain the monoamine neurotransmitters (norepinephrine, serotonin, dopamine, and histamine),

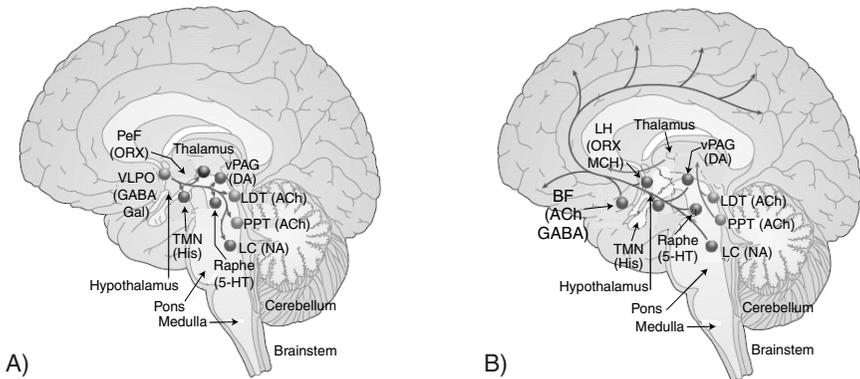


FIGURE 2-3 Sleep-generating (A) and wake-generating (B) systems in the brain. NOTE: Cholinergic (ACh) cell groups; basal forebrain (BF); dopamine (DA); gamma-aminobutyric acid (GABA); galanin (Gal); histamine (His); serotonin (5-HT); locus coeruleus (LC); laterodorsal tegmental nuclei (LDT); lateral hypothalamus (LH); melanin-concentrating hormone (MCH); noradrenaline (NA); orexin (ORX); perifornical (PeF); the pedunculopontine (PPT); tuberomammillary nucleus (TMN); ventrolateral preoptic nucleus (VLPO); ventral periaqueductal gray (vPAG). SOURCE: Saper et al. (2005c).

enters the hypothalamus, rather than the thalamus, where it picks up inputs from nerve cells that contain peptides (orexin or hypocretin and melanin-concentrating hormone). These inputs then traverse the basal forebrain, where they pick up additional inputs from cells containing acetylcholine and gamma-aminobutyric acid. Ultimately, all of these inputs enter the cerebral cortex, where they diffusely activate the nerve cells and prepare them for the interpretation and analysis of incoming sensory information.

CIRCADIAN RHYTHMS, THE 24-HOUR CLOCK

Circadian rhythms refer, collectively, to the daily rhythms in physiology and behavior. They control the sleep-wake cycle, modulate physical activity and food consumption, and over the course of the day regulate body temperature, heart rate, muscle tone, and hormone secretion. The rhythms are generated by neural structures in the hypothalamus that function as a biological clock (Dunlap et al., 2004). Animals and plants possess endogenous clocks to organize daily behavioral and physiological rhythms in accord with the external day-night cycle (Bunning, 1964). The basis for these clocks is believed to be a series of molecular pathways involving “clock” genes that are expressed in a nearly 24-hour rhythm (Vitaterna et al., 2005).

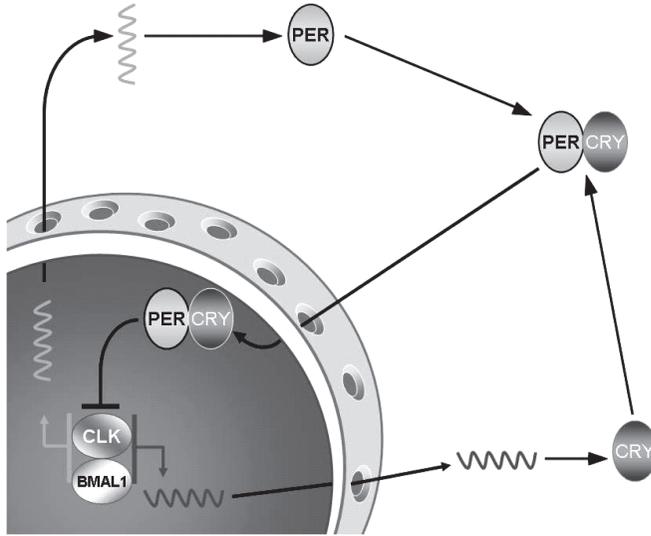


FIGURE 2-4 Molecular mechanisms underlying the activity of the circadian clock. **NOTE:** The activation and deactivation of *Period* and *Cryptochrome* protein production is the basis of a negative-feedback loop that controls the ~24-hour cycle time of circadian clocks. Thus, the ability of the *Period* and *Cryptochrome* proteins to modulate their own production allows the system to self-regulate.

In mammals, two proteins, Clock and Bmal1, bind together and move into the nucleus of the cell, where they bind to specific sites in the DNA that activate specific genes (Figure 2-4). Among the genes that they activate are *Period* and *Cryptochrome*. The products of these genes also move back into the nucleus, where they disrupt the binding of Clock and Bmal1 to the DNA, thus inhibiting their own synthesis. This results in a rising and falling pattern of expression of the *Period* and *Cryptochrome* gene products with a periodicity that is very close to 24 hours.

Many other genes are also regulated by Clock and Bmal1, and these genes cycle in this way in many tissues in the body, giving rise to daily patterns of activity. These rhythmically expressed genes contribute to many aspects of cellular function, including glucose and lipid metabolism, signal transduction, secretion, oxidative metabolism, and many others, suggesting the importance of the circadian system in many central aspects of life.

The Suprachiasmatic Nucleus

The suprachiasmatic nucleus (SCN) is responsible for regulating circadian rhythms in all organs. It receives direct inputs from a class of nerve

cells in the retina that act as brightness detectors, which can reset the clock genes in the SCN on a daily basis. The SCN then transmits to the rest of the brain and body signals that bring all of the daily cycles in synchrony with the external day-night cycle.

The main influence of the SCN on sleep is due to a series of relays through the dorsomedial nucleus of the hypothalamus, which signals to the wake-sleep systems to coordinate their activity with the day-night cycles. The SCN also coordinates cycles of feeding, locomotor activity, and hormones, such as corticosteroids (Chou et al., 2003). Under some conditions (e.g., limited food availability) when there are changes in the external temperature, or even under conditions of behavioral stress (e.g., the need to avoid a predator), animals must shift their daily cycles to survive. In such circumstances, the dorsomedial nucleus may shift to a new daily cycle, which can be completely out of phase with the SCN and the light-dark cycle, and its signals also shift the daily cycles of sleep, activity, feeding, and corticosteroid hormone secretion (Saper et al., 2005b,c).

Another major output of the SCN is to a pathway that controls the secretion of melatonin, a hormone produced by the pineal gland. Melatonin, which is mainly secreted at night, acts to further consolidate the circadian rhythms but has only limited effects directly on sleep.

Sleep and Thermoregulation

Body temperature regulation is subject to circadian system influence. An individual's body temperature is higher during the day than at night (Figure 2-5). At night there is a gradual decline in body temperature, a decrease in heat production (called the falling phase of the body temperature rhythm), and an increase in heat loss, all which promote sleep onset and maintenance, as well as EEG slow-wave activity. Conversely, there is a gradual increase in body temperature several hours before waking. The brain sends signals to other parts of the body that increase heat production and conservation in order to disrupt sleep and promote waking (Szymusiak, 2005).

SLEEP PATTERNS CHANGE WITH AGE

Sleep architecture changes continuously and considerably with age. From infancy to adulthood, there are marked changes in how sleep is initiated and maintained, the percentage of time spent in each stage of sleep, and overall sleep efficiency (i.e., how successfully sleep is initiated and maintained). A general trend is that sleep efficiency declines with age (Figure 2-6). Although the consequences of decreased sleep efficiency are relatively well documented, the reasons are complex and poorly understood. Exami-

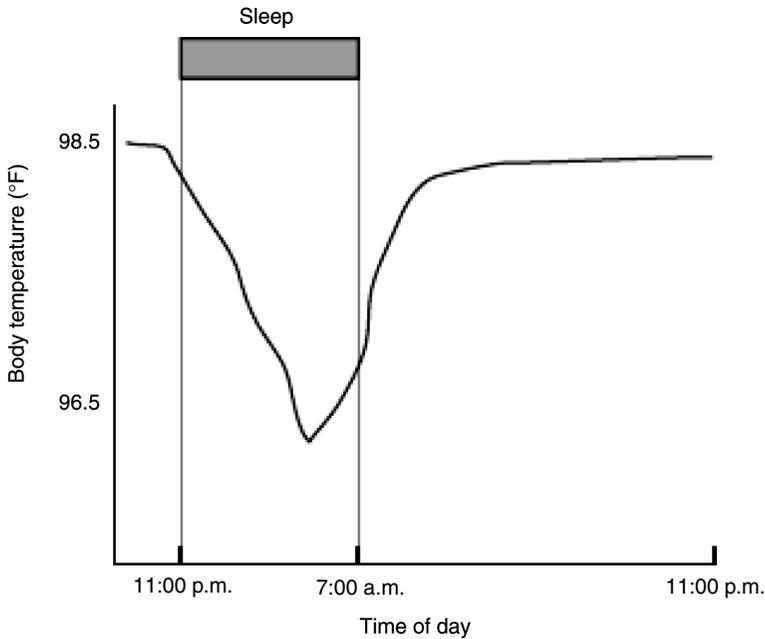


FIGURE 2-5 Body temperature in relation to time of day.
SOURCE: NHBLI (2003).

nation of sleep characteristics by age, however, allows a closer understanding of the function of sleep for human development and successful aging.

Newborns and Infants

At birth, sleep timing is distributed evenly across day and night for the first few weeks, with no regular rhythm or concentration of sleeping and waking. Newborns sleep about 16 to 18 hours per day; however, it is discontinuous with the longest continuous sleep episode lasting only 2.5 to 4 hours (Adair and Bauchner, 1993; Roffwarg et al., 1966). Newborns have three types of sleep: quiet sleep (similar to NREM), active sleep (analogous to REM), and indeterminate sleep (Davis et al., 2004). Sleep onset occurs through REM, not NREM, and each sleep episode consists of only one or two cycles (Jenni and Carskadon, 2000; Davis et al., 2004). This distinctive sleep architecture occurs mostly because circadian rhythms have not yet been fully entrained (Davis et al., 2004).

Circadian rhythms begin to arise around 2 to 3 months of age, leading to sleep consolidation that manifests in greater durations of wakefulness

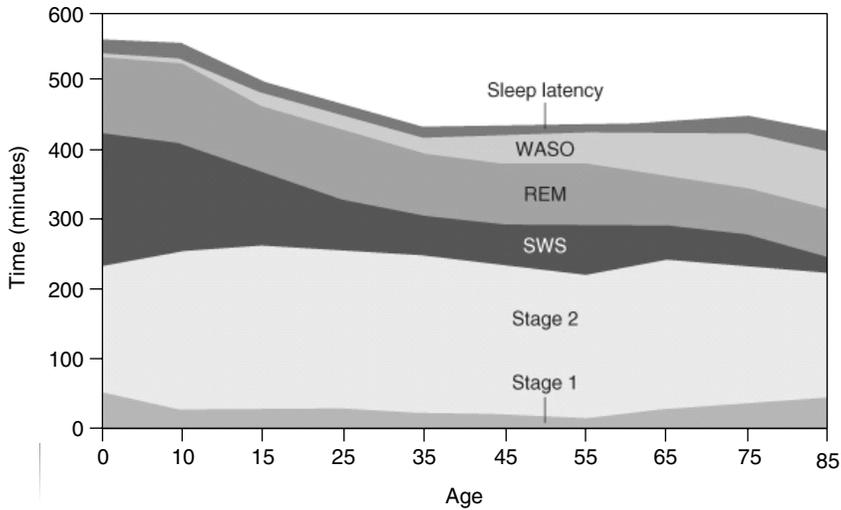


FIGURE 2-6 Changes in sleep with age.

NOTE: Time (in minutes) for sleep latency, amount of time spent awake after initially falling asleep (WASO), rapid eye movement (REM), non-rapid eye movement (NREM), stages 1, 2, and slow-wave sleep (SWS).

SOURCE: Carskadon and Rechtschaffen (2005).

during the day and longer periods of sleep at night (Sheldon, 2002). Circadian rhythm development in the first 3 months includes: emergence of the 24-hour core body temperature cycle (1 month of age); progression of nocturnal sleeping (2 months of age); and cycling of melatonin and cortisol hormones in a circadian rhythm (3 months of age) (Jenni and Carskadon, 2000).

Sleep cycles also change because of the emergence of the circadian rhythm and a greater responsiveness to social cues (such as breast-feeding and bedtime routines). By 3 months of age, sleep cycles become more regular: sleep onset now begins with NREM, REM sleep decreases and shifts to the later part of the sleep cycle, and the total NREM and REM sleep cycle is typically 50 minutes (Anders et al., 1995; Jenni and Carskadon, 2000). By 6 months of age, total sleep time reduces slightly and the longest continuous sleep episode lengthens to approximately 6 hours (Anders et al., 1995; Jenni and Carskadon, 2000). As sleep cycles mature, the typical muscle paralysis of REM sleep replaces the propensity for movement in what was called “active sleep” as a newborn. By 12 months old, the infant typically sleeps 14 to 15 hours per day with the majority of sleep consolidated in the evening and during one to two naps during the day (Anders et al., 1995).

Young Children

There are a limited number of studies that address normal sleep architecture in young children; however, one trend that appears to be consistent is that sleep amounts decrease as a child gets older. The reduction cannot be attributed solely to physiologic requirements, because cultural environments and social changes also influence changing sleep characteristics in young children. Total sleep time decreases by 2 hours from age 2 to age 5 (13 hours to 11) (Roffward et al., 1966). Socially, the decrease in time asleep may be a result of decreased daytime napping, as most children discontinue napping between 3 and 5 years old (Jenni and Carskadon, 2000). Other social and cultural factors that begin to influence sleep include how, with whom, and where children sleep and the introduction of school time routines (Jenni and O'Connor, 2005).

Physiologically, it has been suggested that by the time children enter school (typically 6 years old) they begin to manifest circadian sleep phase preferences—a tendency to be a “night owl” or “morning bird” (Jenni and Carskadon, 2000). Older children, however, are significantly more likely to experience challenges in initiating and maintaining sleep than younger children. In addition, older children are more likely to have nightmares, which usually disrupt sleep, making it discontinuous (Beltramini and Hertzog, 1983). One study found that children appear to have longer REM sleep latencies than adolescents and consequently spend a greater percentage of sleep time in stages 3 and 4 (Gaudreau et al., 2001).

Adolescents

A complex and bidirectional relationship exists between pubertal development and sleep. Studies underscore the importance of using pubertal stage, rather than chronologic age as the metric in understanding sleep, as has been found for other physiologic parameters in the second decade of life. It has been determined that adolescents require 9 to 10 hours of sleep each night (Carskadon et al., 1993; Mercer et al., 1998), though few adolescents obtain adequate sleep. In the United States, the average total sleep time in a sample of eighth-grade students was found to be 7.9 hours (Wolfson et al., 2003). Over a quarter of high school and college students were found to be sleep deprived (Wolfson and Carskadon, 1998).

SWS and sleep latency time progressively declines with advancing pubertal development (Carskadon et al., 1980); however, time spent in stage 2 increases (Carskadon, 1982). These changes are likely in part due to pubertal and hormonal changes that accompany the onset of puberty (Karacan et al., 1975). For instance, at midpuberty, there is significantly greater daytime sleepiness than at earlier stages of puberty. Afternoon

sleepiness is greater than that in late afternoon and evening in more mature adolescents than in younger subjects. With increasing age, the total time spent sleeping decreases, as does REM sleep. However, if bedtime is fixed, the duration of REM sleep remains constant (Carskadon, 1982; Carskadon et al., 1983).

Adults

Sleep architecture continues to change with age across adulthood. Two major attributes of age-related sleep changes are earlier wake time and reduced sleep consolidation (Dijk et al., 2000). A hallmark change with age is a tendency toward earlier bedtimes and wake times. Older adults (approximately ages 65 to 75) typically awaken 1.33 hours earlier, and go to bed 1.07 hours earlier, than younger adults (approximately ages 20 to 30) (Duffy et al., 1998). There are no conclusive studies that demonstrate why older adults experience earlier wake times, despite decreased sleep efficiency, but one hypothesis may be an advanced circadian pacemaker that accompanies age (Dijk et al., 2000). It is unclear if this is due to older adults experiencing an increased sensitivity to light (Dijk et al., 2000; Ancoli-Israel, 2005). Nonetheless, the consequences of an advanced circadian rhythm are a 1-hour advance in body temperature increase in the early morning and misaligned melatonin and cortisol secretion rhythms with the circadian clock (Dijk et al., 2000).

Younger adults may experience brief awakenings, but they are usually minor and occur close to an REM sleep transition; thus, sleep remains relatively consolidated. Arousal occurring mostly from REM sleep in young adults suggests that there is a protective mechanism to keep from awakening during NREM sleep; however, this protective effect appears to also decline with age (Dijk, 1998). As an individual ages (between the ages of 20 to 60), SWS declines at a rate of about 2 percent per decade (Figure 2-6) (Dijk et al., 1989; Astrom and Trojaborg, 1992; Landolt et al., 1996; Ancoli-Israel, 2005). Because arousal thresholds are typically highest during SWS, and because SWS declines with age, older adults experience more frequent awakenings during a sleep episode. Another important variable may be an age-related reduction both in homeostatic sleep pressure and circadian pacemaker effectiveness during the night (Dijk et al., 2000).

Gender Differences

Although there have been few systematic studies, there appear to be gender-based differences in sleep and circadian rhythms. Available evidence is strongest in adults; however, gender differences have also been observed in infancy (Bach et al., 2000; Moss and Robson, 1970; Hoppenbrouwers et

al., 1989), childhood (Meijer et al., 2000; Sadeh et al., 2000; Acebo et al., 1996), and adolescence (Giannotti et al., 2002; Laberge et al., 2001). In adults, men spend greater time in stage 1 sleep (Bixler et al., 1984) and experience more awakenings (Kobayashi et al., 1998). Although women maintain SWS longer than men, they complain more often of difficulty falling asleep and midsleep awakenings. In contrast, men are more likely to complain of daytime sleepiness (Ancoli-Israel, 2000).

In women, the menstrual cycle may influence sleep-wake activity; however, methodological challenges have limited the number of conclusive findings (Metcalfe, 1983; Leibenluft et al., 1994). There have been a number of studies that suggest that women's sleep patterns are greatly affected during pregnancy and the postpartum period (Karacan et al., 1968; Hertz et al., 1992; Lee and Zaffke, 1999; Driver and Shapiro, 1992). For example, women often experience considerable daytime sleepiness during pregnancy and during the first few postpartum months, and as will be discussed in greater detail in Chapter 3, they are also at a higher risk of developing restless legs syndrome (Goodman et al., 1998; Lee et al., 2001).

Elderly People

Problematic sleep has adverse effects on all individuals, regardless of age; however, older people typically show an increase in disturbed sleep that can create a negative impact on their quality of life, mood, and alertness (Ancoli-Israel, 2005; Bliwise, 2005). Elderly individuals sleep 36 percent less than children at age 5 (Figure 2-6). Although the ability to sleep becomes more difficult, the need to sleep does not decrease with age (Ancoli-Israel, 2005). Difficulty in initiating and maintaining sleep is cited in 43 percent of the elderly (Foley et al., 1995), although these problems are more commonly among adults suffering from depression, respiratory symptoms, and physical disability, among others (Ancoli-Israel, 2005). However, declining sleep efficiency and quality has also been observed in healthy older people (Dijk et al., 2000).

Changes in sleep patterns affect males and females differently. The progressive decrease in SWS is one of the most prominent changes with aging; however, it appears to preferentially affect men. The gender difference is unclear, but it has been suggested that older women have "better-preserved" SWS than men (Reynolds et al., 1985). Women ages 70 and older spend around 15 to 20 percent of total sleep time in stages 3 and 4; men of the same age spend only around 5 percent of total sleep time in stages 3 and 4 (Redline et al., 2004). Another gender contrast is that older women go to bed and wake up earlier than older men, which suggests that body temperature rhythms are phase-advanced in elderly women (Campbell et al., 1989;

Moe et al., 1991; Monk et al., 1995). However, both men and women have increased stage 1 and decreased REM sleep.

Older people also experience a decrease in melatonin levels, which may be due to the gradual deterioration of the hypothalamic nuclei that drive circadian rhythms (Ancoli-Israel, 2005). The inability to maintain long sleep episodes and bouts of wakefulness may reflect, in addition to other medical factors, a continuously decreasing sleep homeostasis (Dijk et al., 2000; Bliwise, 2005). Other prominent factors are the continuous increase in sleep latency and nighttime awakenings and inconsistency of external cues such as light exposure (which tends to be low), irregular meal times, nocturia, and decreased mobility leading to a reduction in exercise (Dijk et al., 2000; Ancoli-Israel, 2005; Bliwise, 2005).

REFERENCES

- Acebo C, Millman RP, Rosenberg C, Cavallo A, Carskadon MA. 1996. Sleep, breathing, and cephalometrics in older children and young adults. Part I: Normative values. *Chest* 109(3):664–672.
- Adair RH, Bauchner H. 1993. Sleep problems in childhood. *Current Problems in Pediatrics* 23(4):142,147–170.
- Ancoli-Israel S. 2000. Insomnia in the elderly: A review for the primary care practitioner. *Sleep: Supplement* 23(1): S23–S30, discussion S36–S38.
- Ancoli-Israel S. 2005. Normal human sleep at different ages: Sleep in older adults. In: Sleep Research Society, eds. *SRS Basics of Sleep Guide*. Westchester, IL: Sleep Research Society. Pp. 21–26.
- Anders TF, Sadeh A, Appareddy V. 1995. Normal sleep in neonates and children. In: Ferber RKM, ed. *Principles and Practice of Sleep Medicine in the Child*. Philadelphia: Saunders. Pp. 7–18.
- Astrom C, Trojaborg W. 1992. Relationship of age to power spectrum analysis of EEG during sleep. *Journal of Clinical Neurophysiology* 9(3):424–430.
- Bach V, Telliez F, Leke A, Libert JP. 2000. Gender-related sleep differences in neonates in thermoneutral and cool environments. *Journal of Sleep Research* 9(3):249–254.
- Bader G, Gillberg C, Johnson M, Kadesjö B, Rasmussen P. 2003. Activity and sleep in children with ADHD. *Sleep* 26:A136.
- Beltramini AU, Hertzog ME. 1983. Sleep and bedtime behavior in preschool-aged children. *Pediatrics* 71(2):153–158.
- Bixler EO, Kales A, Jacoby JA, Soldatos CR, Vela-Bueno A. 1984. Nocturnal sleep and wakefulness: Effects of age and sex in normal sleepers. *International Journal of Neuroscience* 23(1):33–42.
- Blasi A, Jo J, Valladares E, Morgan BJ, Skatrud JB, Khoo MC. 2003. Cardiovascular variability after arousal from sleep: Time-varying spectral analysis. *Journal of Applied Physiology* 95(4):1394–1404.
- Bliwise D. 2005. Normal aging. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Saunders. Pp. 24–38.
- Bunning E. 1964. *The Physiological Clock*. Berlin, Germany: Springer-Verlag.
- Buxton OM, Spiegel K, Van Cauter E. 2002. Modulation of endocrine function and metabolism by sleep and sleep loss. In: Lee-Chiong TL, Sateia MJ, Carskadon MA, eds. *Sleep Medicine*. Philadelphia: Hanley & Belfus. Pp. 59–69.

- Campbell SS, Gillin JC, Kripke DF, Erikson P, Clopton P. 1989. Gender differences in the circadian temperature rhythms of healthy elderly subjects: Relationships to sleep quality. *Sleep* 12(6):529–536.
- Carskadon MA. 1982. The second decade. Guilleminault C, ed. *Sleeping and Waking Disorders: Indications and Techniques*. Menlo Park, CA: Addison-Wesley. Pp. 99–125.
- Carskadon M, Dement W. 2005. Normal human sleep: An overview. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier Saunders. Pp. 13–23.
- Carskadon MA, Rechtschaffen A. 2005. Monitoring and staging human sleep. In: Kryger MH, Roth TT, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier Saunders. Pp. 1359–1377.
- Carskadon MA, Harvey K, Duke P, Anders TF, Litt IF, Dement WC. 1980. Pubertal changes in daytime sleepiness. *Sleep* 2(4):453–460.
- Carskadon MA, Orav EJ, Dement WC. 1983. Evolution of sleep and daytime sleepiness in adolescents. In: Guilleminault CLE, ed. *Sleep/Wake Disorders: Natural History, Epidemiology, and Long-Term Evolution*. New York: Raven Press. Pp. 201–216.
- Carskadon MA, Vieira C, Acebo C. 1993. Association between puberty and delayed phase preference. *Sleep* 16(3):258–262.
- Catcheside PG, Chiong SC, Mercer J, Saunders NA, McEvoy RD. 2002. Noninvasive cardiovascular markers of acoustically induced arousal from non-rapid-eye-movement sleep. *Sleep* 25(7):797–804.
- Chou TC, Scammell TE, Gooley JJ, Gaus SE, Saper CB, Lu J. 2003. Critical role of dorsomedial hypothalamic nucleus in a wide range of behavioral circadian rhythms. *Journal of Neuroscience* 23(33):10691–10702.
- Cianci T, Zoccoli G, Lenzi P, Franzini C. 1991. Loss of integrative control of peripheral circulation during desynchronized sleep. *American Journal of Physiology* 261(2 Pt 2): R373–R377.
- Crick F, Mitchison G. 1983. The function of dream sleep. *Nature* 304(5922):111–114.
- Davis KF, Parker KP, Montgomery GL. 2004. Sleep in infants and young children: Part one: Normal sleep. *Journal of Pediatric Health Care* 18(2):65–71.
- Dement W, Kleitman N. 1957a. Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. *Electroencephalography and Clinical Neurophysiology: Supplement* 9(4):673–690.
- Dement T, Kleitman N. 1957b. The relation of eye movements during sleep to dream activity: An objective method for the study of dreaming. *Journal of Experimental Psychology* 53(5):339–346.
- Dijk DCC. 1998. REM sleep as a gate to wakefulness during forced desynchrony in young and older people [abstract]. *Sleep* 21(3):S298.
- Dijk DJ, Beersma DG, van den Hoofdakker RH. 1989. All night spectral analysis of EEG sleep in young adult and middle-aged male subjects. *Neurobiology of Aging* 10(6):677–682.
- Dijk DJ, Duffy JF, Czeisler CA. 2000. Contribution of circadian physiology and sleep homeostasis to age-related changes in human sleep. *Chronobiology International* 17(3): 285–311.
- Douglas, NJ. 2005. Respiratory physiology: Control of ventilation. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier Saunders. Pp. 224–229.
- Driver HS, Shapiro CM. 1992. A longitudinal study of sleep stages in young women during pregnancy and postpartum. *Sleep* 15(5):449–453.
- Duffy JF, Dijk DJ, Klerman EB, Czeisler CA. 1998. Later endogenous circadian temperature nadir relative to an earlier wake time in older people. *American Journal of Physiology* 275(5 Pt 2):R1478–R1487.

- Dunlap JC, Loros JJ, DeCoursey PJ. 2004. *Chronobiology: Biological Timekeeping*. Sunderland, MA: Sinauer Associates.
- Floras JS, Jones JV, Johnston JA, Brooks DE, Hassan MO, Sleight P. 1978. Arousal and the circadian rhythm of blood pressure. *Clinical Science and Molecular Medicine Supplement* 55(4):395s–397s.
- Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, Blazer DG. 1995. Sleep complaints among elderly persons: An epidemiologic study of three communities. *Sleep* 18(6):425–432.
- Gais S, Molle M, Helms K, Born J. 2002. Learning-dependent increases in sleep spindle density. *Journal of Neuroscience* 22(15):6830–6834.
- Gaudreau H, Carrier J, Montplaisir J. 2001. Age-related modifications of NREM sleep EEG: From childhood to middle age. *Journal of Sleep Research* 10(3):165–172.
- Giannotti F, Cortesi F, Sebastiani T, Ottaviano S. 2002. Circadian preference, sleep and daytime behaviour in adolescence. *Journal of Sleep Research* 11(3):191–199.
- Gillette M, Abbott S. 2005. Fundamentals of the circadian system. In: Sleep Research Society, eds. *SRS Basics of Sleep Guide*. Westchester, IL: Sleep Research Society. Pp. 131–138.
- Goodman JD, Brodie C, Ayida GA. 1988. Restless leg syndrome in pregnancy. *British Medical Journal* 297(6656):1101–1102.
- Hertz G, Fast A, Feinsilver SH, Albertario CL, Schulman H, Fein AM. 1992. Sleep in normal late pregnancy. *Sleep* 15(3):246–251.
- Hoppenbrouwers T, Hodgman J, Arakawa K, Sterman MB. 1989. Polysomnographic sleep and waking states are similar in subsequent siblings of SIDS and control infants during the first six months of life. *Sleep* 12(3):265–276.
- Jenni OG, Carskadon MA. 2000. Normal human sleep at different ages: Infants to adolescents. In: Sleep Research Society, eds. *SRS Basics of Sleep Guide*. Westchester, IL: Sleep Research Society. Pp. 11–19.
- Jenni OG, O'Connor BB. 2005. Children's sleep: An interplay between culture and biology. *Pediatrics* 115(1 Suppl):204–216.
- Jones BE. 2005. Basic mechanisms of sleep-wake states. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 136–153.
- Karacan IH, Agnew H, Williams RL, Webb W, Ross J. 1968. Characteristics of sleep patterns during late pregnancy and postpartum periods. *American Journal of Obstetrics and Gynecology* 297(6656):1101–1102.
- Karacan I, Anch M, Thornby JI, Okawa M, Williams RL. 1975. Longitudinal sleep patterns during pubertal growth: Four-year follow up. *Pediatrics Research* 9(11):842–846.
- Kobayashi R, Kohsaka M, Fukuda N, Honma H, Sakakibara S, Koyama, T. 1998. Gender differences in the sleep of middle-aged individuals. *Psychiatry and Clinical Neurosciences* 52(2):186–187.
- Krieger J. 2000. Respiratory physiology: Breathing in normal subjects. In: Kryger M, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier Saunders. Pp. 229–241.
- Laberge L, Petit D, Simard C, Vitaro F, Tremblay RE, Montplaisir J. 2001. Development of sleep patterns in early adolescence. *Journal of Sleep Research* 10(1):59–67.
- Landolt HP, Dijk DJ, Achermann P, Borbely AA. 1996. Effect of age on the sleep EEG: Slow-wave activity and spindle frequency activity in young and middle-aged men. *Brain Research* 738(2):205–212.
- Lee KA, Zaffke ME. 1999. Longitudinal changes in fatigue and energy during pregnancy and the postpartum period. *Journal of Obstetric, Gynecologic, and Neonatal Nursing* 28(2):183–191.

- Lee KA, Zaffke ME, Baratte-Beebe K. 2001. Restless legs syndrome and sleep disturbance during pregnancy: The role of folate and iron. *Journal of Women's Health and Gender-based Medicine* 10(4):335–341.
- Leibenluft E, Fiero PL, Rubinow DR. 1994. Effects of the menstrual cycle on dependent variables in mood disorder research. *Archives of General Psychiatry* 51(10):761–781.
- Loomis AL, Harvey EN, Hobart GA. 1937. Cerebral states during sleep as studied by human brain potentials. *Journal of Experimental Psychology* 21(2):127–144.
- Lugaresi E, Coccagna G, Cirignotta F, Farneti P, Gallassi R, Di Donato G, Verucchi P. 1978. Breathing during sleep in man in normal and pathological conditions. *Advances in Experimental Medicine and Biology* 99:35–45.
- Madsen PL, Holm S, Vorstrup S, Friberg L, Lassen NA, Wildschiodtz G. 1991a. Human regional cerebral blood flow during rapid-eye-movement sleep. *Journal of Cerebral Blood Flow Metabolism* 11(3):502–507.
- Madsen PL, Schmidt JF, Wildschiodtz G, Friberg L, Holm S, Vorstrup S, Lassen N A. 1991b. Cerebral O₂ metabolism and cerebral blood flow in humans during deep and rapid-eye-movement sleep. *Journal of Applied Physiology* 70(6):2597–2601.
- Meijer AM, Habekothé HT, Van Den Wittenboer GL. 2000. Time in bed, quality of sleep and school functioning of children. *Journal of Sleep Research* 9(2):145–153.
- Mercer PW, Merritt SL, Cowell JM. 1998. Differences in reported sleep need among adolescents. *Journal of Adolescent Health* 23(5):259–263.
- Metcalfe MG. 1983. Incidence of ovulation from the menarche to the menopause: Observations of 622 New Zealand women. *The New Zealand Medical Journal* 96(738): 645–648.
- Moe KE, Prinz PN, Vitiello MV, Marks AL, Larsen LH. 1991. Healthy elderly women and men have different entrained circadian temperature rhythms. *Journal of the American Geriatrics Society* 39(4):383–387.
- Monk TH, Buysse DJ, Reynolds CF III, Kupfer DJ, Houck PR. 1995. Circadian temperature rhythms of older people. *Experimental Gerontology* 30(5):455–474.
- Moruzzi G, Magoun HW. 1949. Brain stem reticular formation and activation of the EEG. *Electroencephalography and Clinical Neurophysiology* 1:455–473.
- Moss HA, Robson KS. 1970. The relation between the amount of time infants spend at various states and the development of visual behavior. *Child Development* 41(2):509–517.
- Mulcahy D, Wright C, Sparrow J, Cunningham D, Curcher D, Purcell H, Fox K. 1993. Heart rate and blood pressure consequences of an afternoon SIESTA (Snooze-Induced Excitation of Sympathetic Triggered Activity). *American Journal of Cardiology* 71(7):611–614.
- NHLBI (National Heart, Lung, and Blood Institute). 2003. *Sleep, Sleep Disorders, and Biological Rhythms: NIH Curriculum Supplement Series, Grades 9-12*. Colorado Springs, CO: Biological Sciences Curriculum Study.
- NLM (National Library of Medicine), NIH (National Institutes of Health). *Medline Plus Online Medical Dictionary*. [Online]. Available: <http://www.nlm.nih.gov/medlineplus/mplustictionary.html> [accessed February 6, 2006].
- Parker KP, Dunbar SB. 2005. Cardiac nursing. In: Woods SL, Froelicher ESS, Motzer SU, Bridges E, eds. *Sleep*. 5th ed. Philadelphia: Lippincott Williams and Wilkins. Pp. 197–219.
- Redline S, Kirchner HL, Quan SF, Gottlieb DJ, Kapur V, Newman A. 2004. The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. *Archives of Internal Medicine* 164(4):406–418.
- Reynolds CF III, Kupfer DJ, Taska LS, Hoch CC, Sewitch DE, Spiker DG. 1985. Sleep of healthy seniors: A revisit. *Sleep* 8(1):20–29.
- Roffward HP, Muzio JN, Dement WC. 1966. Ontogenetic development of the human sleep-dream cycle. *Science* 152(3722):604–619.
- Sadeh A, Raviv A, Gruber R. 2000. Sleep patterns and sleep disruptions in school-age children. *Developmental Psychology* 36(3):291–301.

- Saper CB, Cano G, Scammell TE. 2005a. Homeostatic, circadian, and emotional regulation of sleep. *Journal of Comparative Neurology* 493(1):92–98.
- Saper CB, Lu J, Chou TC, Gooley J. 2005b. The hypothalamic integrator for circadian rhythms. *Trends in Neuroscience* 28(3):152–157.
- Saper CB, Scammell TE, Lu J. 2005c. Hypothalamic regulation of sleep and circadian rhythms. *Nature* 437(7063):1257–1263.
- Sheldon SH. 2002. Sleep in infants and children. In: Lee-Chiong TK, Sateia MJ, Carskadon MA, eds. *Sleep Medicine*. Philadelphia: Hanley and Belfus. Pp. 99–103.
- Simon PM, Landry SH, Leifer JC. 2002. Respiratory control during sleep. In: Lee-Chiong TK, Sateia MJ, Carskadon MA, eds. *Sleep Medicine*. Philadelphia: Hanley and Belfus. Pp. 41–51.
- Smith C, Lapp L. 1991. Increases in number of REMS and REM density in humans following an intensive learning period. *Sleep* 14(4):325–330.
- Somers V, Dyken M, Mark A, Abboud F. 1993. Sympathetic-nerve activity during sleep in normal subjects. *New England Journal of Medicine* 328(5):303–307.
- Szymusiak R. 2005. Thermoregulation and sleep. In: Sleep Research Society, eds. *SRS Basics of Sleep Guide*. Westchester, IL: Sleep Research Society. Pp. 119–126.
- Tank J, Diedrich A, Hale N, Niaz FE, Furlan R, Robertson RM, Mosqueda-Garcia R. 2003. Relationship between blood pressure, sleep K-complexes, and muscle sympathetic nerve activity in humans. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* 285(1):R208–R214.
- Van Cauter E. 2000. Endocrine physiology. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. Philadelphia: Elsevier/Saunders. Pp. 266–278.
- Vitaterna M, Pinto L, Turek F. 2005. Molecular genetic basis for mammalian circadian rhythms. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 363–374.
- Wolfson AR, Carskadon MA. 1998. Sleep schedules and daytime functioning in adolescents. *Child Development* 69(4):875–887.
- Wolfson AR, Carskadon MA, Acebo C, Seifer R, Fallone G, Labyak SE, Martin JL. 2003. Evidence for the validity of a sleep habits survey for adolescents. *Sleep* 26(2):213–216.
- Zepelin H, Siegel JM, Tobler I. 2005. Mammalian sleep. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 91–100.

3

Extent and Health Consequences of Chronic Sleep Loss and Sleep Disorders

CHAPTER SUMMARY *It is estimated that 50 to 70 million Americans chronically suffer from a disorder of sleep and wakefulness, hindering daily functioning and adversely affecting health and longevity. There are around 90 distinct sleep disorders; most are marked by one of these symptoms: excessive daytime sleepiness, difficulty initiating or maintaining sleep, and abnormal events occurring during sleep. The cumulative long-term effects of sleep loss and sleep disorders have been associated with a wide range of deleterious health consequences including an increased risk of hypertension, diabetes, obesity, depression, heart attack, and stroke. After decades of research, the case can be confidently made that sleep loss and sleep disorders have profound and widespread effects on human health. This chapter focuses on manifestations and prevalence, etiology and risk factors, and comorbidities of the most common sleep conditions, including sleep loss, sleep-disordered breathing, insomnia, narcolepsy, restless legs syndrome, parasomnias, sleep-related psychiatric disorders, sleep-related neurological disorders, sleep-related medical disorders, and circadian rhythm sleep disorders.*

Sleep loss and sleep disorders are among the most common yet frequently overlooked and readily treatable health problems. It is estimated that 50 to 70 million Americans chronically suffer from a disorder of sleep and wakefulness, hindering daily functioning and adversely affecting health and longevity (NHLBI, 2003). Questions about sleep are seldom asked by physicians (Namen et al., 1999, 2001). For example, about 80 to 90 percent of adults with clinically significant sleep-disordered breathing remain undiagnosed (Young et al., 1997b). Failure to recognize sleep problems not only precludes diagnosis and treatment—it also precludes the possibility of preventing their grave public health consequences.

The public health consequences of sleep loss and sleep-related disorders are far from benign. The most visible consequences are errors in judgment contributing to disastrous events such as the space shuttle *Challenger* (Walsh et al., 2005). Less visible consequences of sleep conditions are far more prevalent, and they take a toll on nearly every key indicator of public health: mortality, morbidity, performance, accidents and injuries, functioning and quality of life, family well-being, and health care utilization. Some of these consequences, such as automobile crashes, occur acutely within hours (or minutes) of the sleep disorder, and thus are relatively easy to link to sleep problems. Others—for example, obesity and hypertension—develop more insidiously over months and years of chronic sleep problems. After decades of research, the case can be confidently made that sleep loss and sleep disorders have profound and widespread effects on human health.

Although there are around 90 distinct sleep disorders, according to the International Classification of Sleep Disorders (AASM, 2005), most are marked by one of these symptoms: excessive daytime sleepiness, difficulty initiating or maintaining sleep, or abnormal movements, behaviors, and sensations occurring during sleep. The cumulative effects of sleep loss and sleep disorders have been associated with a wide range of deleterious health consequences including an increased risk of hypertension, diabetes, obesity, depression, heart attack, and stroke.

This chapter focuses on the most common sleep conditions, including sleep loss, sleep-disordered breathing, insomnia, narcolepsy, restless legs syndrome (RLS), parasomnias, sleep-related psychiatric disorders, sleep-related neurological disorders, sleep-related medical disorders, and circadian rhythm sleep disorders. The manifestations and prevalence, etiology and risk factors, and comorbidities for each condition are briefly described. There is a large body of data on these disorders, in part because they encompass the most frequently cited sleep disorders or they carry the greatest public health burden. As such, the committee chose to focus primarily on these disorders.

SLEEP LOSS

Manifestations and Prevalence

Sleep loss generally, in adults, refers to sleep of shorter duration than the average basal need of 7 to 8 hours per night. The main symptom of sleep loss is excessive daytime sleepiness, but other symptoms include depressed mood and poor memory or concentration (Dinges et al., 2005). Chronic sleep loss, while neither a formal syndrome nor a disorder, has serious consequences for health, performance, and safety, as described in Chapter 4.

Sleep loss is a highly prevalent problem that continues to worsen in frequency as individuals grow older. Recent studies find that at least 18 percent of adults report receiving insufficient sleep (Liu et al., 2000; Kapur et al., 2002; Strine and Chapman, 2005). Historically, there have been a limited number of nationally representative surveys that provide reliable data on sleep patterns in the population. The National Health Interview Survey (NHIS), run by the Centers for Disease Control and Prevention (CDC) (see Chapter 5), included the following question in the 1977, 1985, 1990 cycles: “On average how many hours of sleep do you get a night (24-hour period)?” The same question was added to the core NHIS questionnaire in 2004. Based on these data, it has been estimated that the percentage of men and women who sleep less than 6 hours has increased significantly over the last 20 years (Figure 3-1) (CDC, 2005). More than 35 years ago, adults reported sleeping 7.7 hours per night (Tune, 1968).

Adolescents also frequently report receiving insufficient sleep. Contrary to public perceptions, adolescents need as much sleep as preteens. A large survey of over 3,000 adolescents in Rhode Island found that only 15 percent reported sleeping 8.5 or more hours on school nights, and 26 percent reported sleeping 6.5 hours or less (Wolfson and Carskadon, 1998). The optimal sleep duration for adolescents, about 9 hours per night, is based on research about alertness, sleep-wake cycles, hormones, and circadian rhythms (Carskadon et al., 2004). Among adolescents, extensive television viewing and growing social, recreational, and academic demands contribute to sleep loss or sleep problems (Wolfson and Carskadon, 1998; Johnson et al., 2004).

Etiology and Risk Factors

The causes of sleep loss are multifactorial. They fall under two major, somewhat overlapping categories: lifestyle/occupational (e.g., shift work,¹

¹The term “shift work” is defined by regular employment outside of the normal day work hours of 7:00 a.m. to 6:00 p.m.

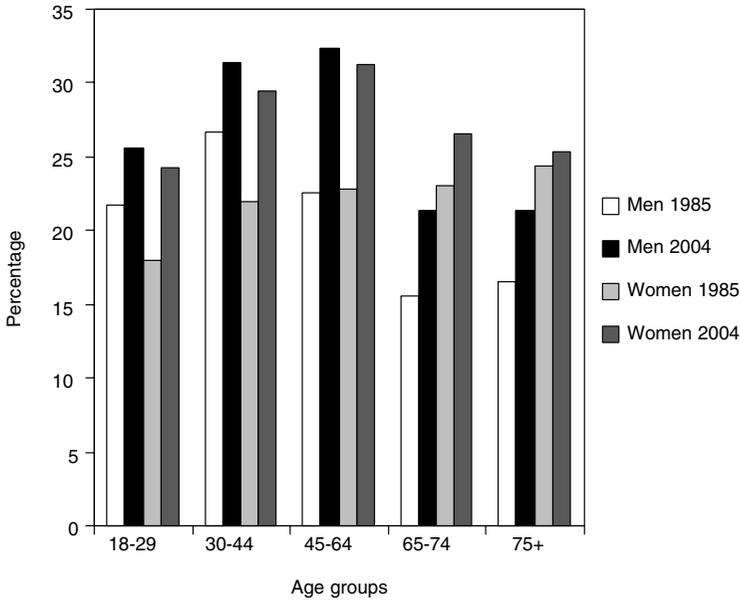


FIGURE 3-1 Percent of adults in the United States who usually slept 6 hours or less a night.

SOURCE: CDC (2005).

prolonged working hours, jet lag, irregular sleep schedules²), and sleep disorders (e.g., insomnia, sleep-disordered breathing, RLS, narcolepsy, and circadian rhythm disorders). Unfortunately, available epidemiological data are not sufficient to determine the extent to which sleep loss is caused by pathology versus behavioral components. The increase in sleep loss is driven largely by broad societal changes, including greater reliance on longer work hours, shift work, and greater access to television and the Internet. About 20 percent of workers are engaged in some kind of shift work (Monk, 2005), of whom there is a growing number of night shift workers suffering chronic sleep loss and disruption of circadian rhythms (Harma et al., 1998; Drake et al., 2004). One indication of the growing trend is the number of adults departing for work between midnight and 5:30 a.m.; that number has grown, over a 10-year period, by 24 percent (United States Census Bureau, 1990). A greater prevalence of insomnia also may contribute to the rise in sleep loss, but probably to a lesser extent than do occupational or lifestyle

²Irregular sleep schedules frequently include significant disparities between sleep on weekdays and weekends, which contribute to shifts in sleep phase and sleep problems.

changes. Adults are sleeping less to get more work accomplished and are staying up later to watch television or use the Internet (NSF, 2005b).

Sleep Loss Affects Health

In the past 10 or more years, research has overturned the dogma that sleep loss has no health effects, apart from daytime sleepiness. The studies discussed in this section suggest that sleep loss (less than 7 hours per night) may have wide-ranging effects on the cardiovascular, endocrine, immune, and nervous systems, including the following:

- Obesity in adults and children
- Diabetes and impaired glucose tolerance
- Cardiovascular disease and hypertension
- Anxiety symptoms
- Depressed mood
- Alcohol use

Many of the studies find graded associations, insofar as the greater the degree of sleep deprivation, the greater the apparent adverse effect (although the difference may not reach statistical significance). Another common finding is the relationship that adverse effects occur with either short or long sleep duration, as compared to a sleep time of 7 to 8 hours. This type of association is often described as a U-shaped relationship. It should be noted, however, that the majority of these studies are observational in nature, and thus definite causal inferences cannot be made. The associations observed in some studies might be subject to different types of biases, such as temporal (or “reverse causality”) bias, whereby sleep loss might be a *manifestation* or a *symptom* of the disease in question. The latter is most likely in cross-sectional studies but could also affect associations observed in cohort studies, particularly when they are relatively short term and/or when the disease under investigation has a long preclinical phase. In the discussion that follows, and wherever possible, potential physiological mechanisms behind epidemiological associations and that support the plausibility of a true causal relationship are noted.

Sleep Loss Is Associated with Obesity

When a person sleeps less than 7 hours a night there is a dose-response relationship between sleep loss and obesity: the shorter the sleep, the greater the obesity, as typically measured by body mass index (BMI)—weight in kilograms divided by height in meters squared. Although most studies were cross-sectional, one prospective study was a 13-year cohort study of nearly

500 adults. By age 27, individuals with short sleep duration (less than 6 hours) were 7.5 times more likely to have a higher body mass index, after controlling for confounding factors such as family history, levels of physical activity, and demographic factors (Hasler et al., 2004). Another study, a large population-based study of more than 1,000 adults, found a U-shaped relationship between sleep duration, measured by polysomnography, and BMI (Figure 3-2). Adults who slept 7.7 hours had the lowest BMI; those with shorter and longer sleep duration had progressively higher BMI. The U-shaped association also applies to other health outcomes, such as heart attacks. The impact of sleep loss diminishes with age. The study also sought to investigate physiological mechanisms behind the relationship between sleep duration and BMI. Measuring two appetite-related hormones, the study found that sleep insufficiency increased appetite. Sleep insufficiency was associated with lower levels of leptin, a hormone produced by an adipose tissue hormone that suppresses appetite, and higher levels of ghrelin, a peptide that stimulates appetite (Taheri et al., 2004). Another study—a small randomized, cross-over clinical trial—also found that sleep restriction was associated with lower leptin and higher ghrelin levels (Spiegel et al., 2004). The findings suggest that a hormonally mediated increase in appetite may help to explain why short sleep is related to obesity. Several mediating mechanisms have been proposed, including effects of sleep deprivation on

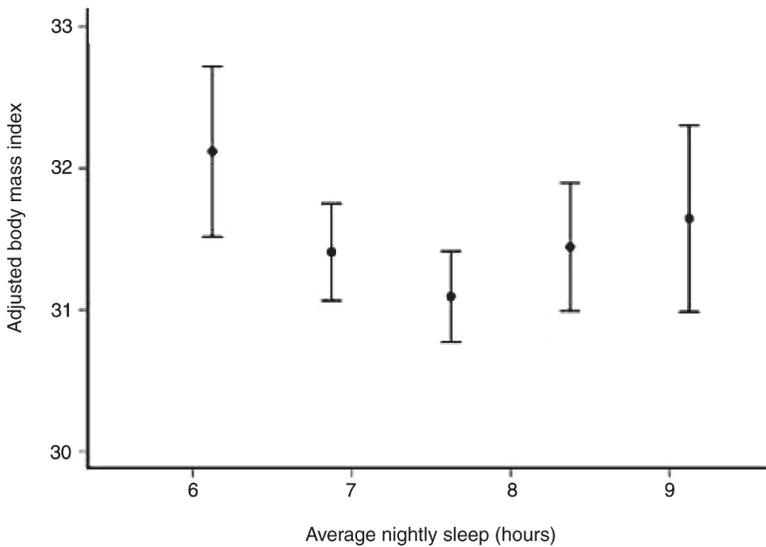


FIGURE 3-2 Curvilinear relationship between BMI and average nightly sleep.
SOURCE: Taheri et al. (2004).

the sympathetic nervous system and/or hypothalamic hormones (Spiegel et al., 2004), which also influence appetite.

Obesity also contributes to obstructive sleep apnea (OSA). This most likely occurs through fat deposition in airways, causing them to narrow. This point is inferred from studies finding that large neck size is a better predictor of OSA than is BMI (Katz et al., 1990) and the finding that central obesity (obesity around the waist) is a better predictor of OSA than total obesity (Grunstein, 2005b). The relationship has been found in well-designed epidemiological studies of young children (Locard et al., 1992; Sekine et al., 2002; von Kries et al., 2002) and adults (Vioque et al., 2000; Kripke et al., 2002; Gupta et al., 2002; Taheri et al., 2004; Hasler et al., 2004).

Taken as a whole, the body of evidence suggests that the serious public health problem of obesity may continue to grow as sleep loss trends continue to worsen. It also suggests that addressing obesity will likely benefit sleep disorders, and treating sleep deprivation and sleep disorders may benefit individuals with obesity (Taheri et al., 2004).

Sleep Loss Is Associated with Diabetes and Impaired Glucose Tolerance

Two large epidemiological studies and one experimental study found an association between sleep loss and diabetes, or impaired glucose tolerance. Impaired glucose tolerance, which is a precursor to diabetes, is manifested by glucose levels rising higher than normal and for a longer period after an intravenous dose of glucose. In the Sleep Heart Health Study, which is a community-based cohort, adults (middle-aged and older) who reported 5 hours of sleep or less were 2.5 times more likely to have diabetes, compared with those who slept 7 to 8 hours per night (Figure 3-3, [Gottlieb et al., 2005]). Those reporting 6 hours per night were about 1.7 times more likely to have diabetes. Both groups were also more likely to display impaired glucose tolerance. Adults with sleep times of 9 hours or more also showed these effects, a finding consistent with the Nurses Health Study. Adjustment for waist girth, a measure of obesity, did not alter the significance of the findings, suggesting that the diabetes effect was independent of obesity.

The relationship between shorter sleep times and impaired glucose tolerance is also supported by an experimental study in which 11 healthy male volunteers were restricted to 4 hours of sleep for a total of six nights (Spiegel et al., 1999). Even after this relatively short period of time, the study found that sleep loss, compared with a fully rested state, led to impaired glucose tolerance. The effect resolved after restoring sleep to normal. Glucose clearance was 40 percent slower with sleep loss than with sleep recovery. Further, mice that have a mutation in a gene that regulates

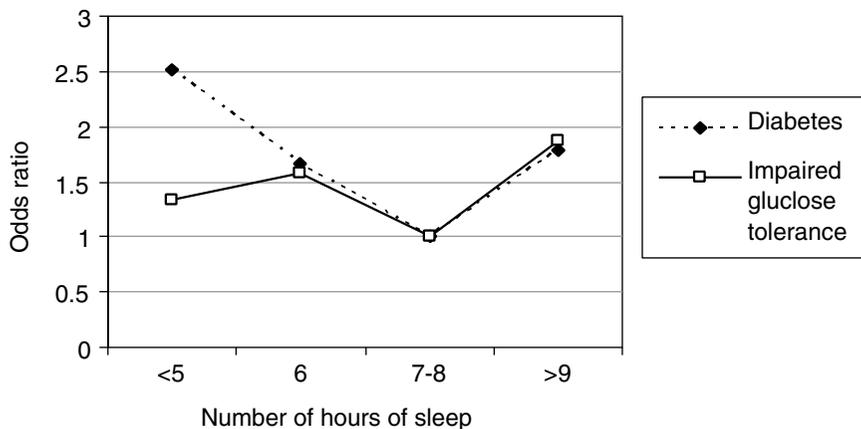


FIGURE 3-3 Sleep duration impacts prevalence of diabetes.

NOTE: Data were adjusted for age, sex, race, waist girth, caffeine, alcohol, smoking, and apnea-hypopnea index.

SOURCE: Gottlieb et al. (2005).

circadian rhythms have metabolic disorders (Turek et al., 2005). The association between sleep loss and diabetes or impaired glucose tolerance may mediate the relationship between sleep loss and cardiovascular morbidity and mortality, as discussed below.

Sleep Loss Is Associated with Cardiovascular Morbidity

Sleep loss and sleep complaints are associated with heart attacks (myocardial infarction) and perhaps stroke, according to several large epidemiological studies (Eaker et al., 1992; Qureshi et al., 1997; Schwartz et al., 1998; Newman et al., 2000; Ayas et al., 2003; Yaggi et al., 2005; Bradley et al., 2005; Caples et al., 2005) and one case-control study (Liu et al., 2002). One of these studies, of incident cases of heart attacks in the Nurses Health Study, was discussed earlier because it also found increased incidence of diabetes (Ayas et al., 2003). The cohort had no coronary heart disease at baseline. Ten years later, in 1996, the likelihood of nonfatal and fatal heart attack was modestly increased for both short and long sleep duration. Five hours of sleep or less was associated with a 45 percent increase in risk (odds ratio [OR] = 1.45, 95% confidence interval [CI], 1.10–1.92), after adjusting for age, BMI, smoking, and snoring. Similarly elevated risks were also found for sleeping 9 hours or more. The effects were independent of a history of hypertension or diabetes because additional adjustment for these

conditions yielded slightly lower, but still significantly elevated, relative risks.

Several potential mechanisms could explain the link between sleep loss and cardiovascular events, including blood pressure increases, sympathetic hyperactivity, or impaired glucose tolerance. Experimental data, showing that acute sleep loss (3.6 hours sleep) for one night results in increased blood pressure in healthy young males, may provide a biological mechanism for the observed associations between sleep loss and cardiovascular disease (Tochikubo et al., 1996; Meier-Ewert et al., 2004).

Sleep Loss, Mood, Anxiety, and Alcohol Use

Sleep loss is associated with adverse effects on mood and behavior. Adults with chronic sleep loss report excess mental distress, depressive symptoms, anxiety, and alcohol use (Baldwin and Daugherty, 2004; Strine and Chapman, 2005; Hasler et al., 2005). A meta-analysis of 19 original articles found that partial sleep deprivation alters mood to an even greater extent that it does cognitive or motor functions (Pilcher and Huffcutt, 1996).

Several studies of adolescents, including one with more than 3,000 high school students, found that inadequate sleep is associated with higher levels of depressed mood, anxiety, behavior problems, alcohol use (Carskadon, 1990; Morrison et al., 1992; Wolfson and Carskadon, 1998), and attempted suicide (Liu, 2004). Nevertheless, it is not clear from cross-sectional studies whether sleep influences mood or anxiety level, or vice versa. On the other hand, a large, 3-year longitudinal study of more than 2,200 middle school students (ages 11 to 14) found that self-reported sleep loss was associated with more depressive symptoms and lower self-esteem over time (Fredriksen et al., 2004). The study measured sleep loss using a single question about sleep duration on school nights and measured depressive symptoms and self-esteem by the Children's Depressive Inventory and the Self-Esteem Questionnaire, respectively. Therefore, although this study suggests an association, the evidence is still limited.

Sleep Loss and Disease Mortality

Sleep loss is also associated with increased age-specific mortality, according to three large, population-based, prospective studies (Kripke et al., 2002; Tamakoshi et al., 2004; Patel et al., 2004). The studies were of large cohorts, ranging from 83,000 to 1.1 million people. In three studies, respondents were surveyed about their sleep duration, and then they were followed for periods ranging from 6 to 14 years. Deaths in short or long sleepers were compared with those who slept 7 hours (the reference group), after adjusting for numer-

ous health and demographic factors. Sleeping 5 hours or less increased mortality risk, from all causes, by roughly 15 percent. The largest American study, depicted in Figure 3-4, graphically illustrates what has been found in all three studies: a U-shaped curve, showing that progressively shorter or longer sleep duration is associated with greater mortality. Other epidemiological studies suggest that sleep-loss-related mortality is largely from acute heart attacks (Ayas et al., 2003). Potential pathophysiological mechanisms accounting for the relationship, while poorly understood, have become the focus of growing interest and are discussed later in this chapter.

Management and Treatment

Management and treatment of sleep loss are rarely addressed by clinicians, despite the large toll on society (Chapters 4, 5, and 7). There are no formal treatment guidelines in primary or specialty care for dealing with sleep loss (Dinges et al., 1999). The most effective treatment for sleep loss is to sleep longer or take a short nap lasting no more than 2 hours (Veasey et al., 2002), and to have a better understanding of proper sleep habits. Catching up on sleep on the weekends—a popular remedy for sleep loss—does not return individuals to baseline functioning (Szymczak et al., 1993; Dinges et al., 1997; Klerman and Dijk, 2005; Murdey et al., 2005). If extended work hours or shift work cannot be avoided, specific behavioral tips to stay alert are available (NSF, 2005c), as are such wake-promoting

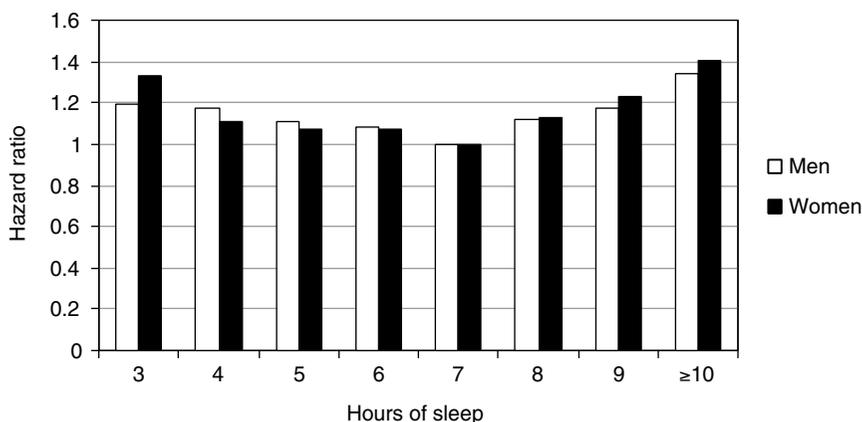


FIGURE 3-4 Shorter or longer sleep duration is associated with greater mortality. NOTE: Hazard ratio is an individual's relative risk of dying compared to the general population, based upon average number of hours of sleep per night. SOURCE: Kripke et al. (2002).

medications as caffeine, modafinil, and sympathomimetic medications (direct and indirect acting), including pemoline and methylphenidate (Mitler and O'Malley, 2005). In a randomized clinical trial caffeine and modafinil showed similar benefits for performance and alertness (Wesensten et al., 2002). Modafinil is the only FDA-approved drug for shift work sleep disorder, although it is not approved for sleep loss. Behavioral approaches developed for insomnia also may be useful for sleep loss, but no formal studies have been undertaken expressly for sleep loss. Furthermore, there have been no large-scale clinical trials examining the safety and efficacy of modafinil, or other drugs, in children and adolescents.

SLEEP-DISORDERED BREATHING

Manifestations and Prevalence

Sleep-disordered breathing refers to a spectrum of disorders that feature breathing pauses during sleep. The most common disorder is characterized by obstructive apneas and hypopneas (White, 2005), where repeated episodes of collapse (apneas) or partial collapse of the pharyngeal airway occur, usually a result of obstruction by soft tissue in the rear of the throat. Snoring, which is produced by vibrations of the soft tissues, is a good marker for OSA (Netzer, et al., 2003). Apneas or hypopneas (a reduction without cessation in airflow or effort) typically result in abrupt and intermittent reduction in blood oxygen saturation, which leads to sleep arousal, often accompanied by loud snorts or gasps as breathing resumes. Episodic interruptions of breathing also frequently cause cortical and brainstem arousals, interrupting sleep continuity, reducing sleep time, and causing increased sympathetic nervous system activation. These broad systemic effects on gas exchange and nervous system activation may lead to a range of systemic effects that affect vascular tone, levels of inflammatory mediators, and hormonal changes. As discussed in the following sections, these in turn may contribute to the development of hypertension, coronary artery disease, congestive heart failure, arrhythmias, stroke, glucose intolerance, and diabetes.

The defining symptom of sleep-disordered breathing is excessive daytime sleepiness. The symptom is likely influenced by sleep fragmentation tied to recurrent arousals that occur in response to breathing pauses. Other symptoms of fragmented sleep include decreased concentration and mood changes. The diagnosis of OSA requires detection, by polysomnography, of at least five or more apneas or hypopneas per hour of sleep (Thorpy, 2005). This rate is expressed as an index, the apnea-hypopnea index (or respiratory disturbance index), which is the average hourly number of apneas plus hypopneas.

OSA is found in at least 4 percent of men and 2 percent of women in the middle-aged workforce, according to the first major United States population-based study of the condition conducted about 15 years ago (Young et al., 1993). Those prevalence figures are based on a cutoff apnea-hypopnea index of 5 or higher, plus a requirement for daytime sleepiness. The prevalence is higher, 9 percent of women and 24 percent of men, with the same apnea-hypopnea index cutoff (Box 3-1), but without the daytime sleepiness requirement. In view of the epidemic increase of obesity (an important determinant of OSA) in recent years, these numbers might underestimate the current prevalence. However, other more recent population-based studies support these prevalence figures (Bixler et al., 1998, 2001).

OSA prevalence appears to increase with age. Adults 65 to 90 years of age had a threefold higher prevalence rate than middle-aged adults (Ancoli-Israel et al., 1991), while the prevalence in children has been reported to be around 2 percent (Ali et al., 1993; Rosen et al., 2003), with higher estimates occurring in ethnic minorities (Gislason and Benediktsdottir, 1995; Redline et al., 1999; Rosen et al., 2003). Underdiagnosis of OSA is common, with between 10 and 20 percent of OSA being diagnosed in adults (Young et al., 1997b). Less than 1 percent of older adults in primary care are referred for polysomnography (Haponik, 1992), although these numbers might have increased in recent years due to increased awareness of the disease. Similarly, children's OSA often goes undiagnosed too, partly because the implications of snoring are not often recognized by pediatricians. Although OSA can occur in children of any age, it is most common at preschool ages, a time coincident with tonsils and adenoids being largest relative to the underlying airway (Jeans et al., 1981).

Obstructive Sleep Apnea Causes Hypertension

OSA causes chronic elevation in daytime blood pressure (Young et al., 2002a; Young and Javaheri, 2005). The strongest evidence for a rise in systemic hypertension comes from several large, well-designed epidemiological studies, both cross-sectional (Young et al., 1997a; Nieto et al., 2000; Bixler et al., 2000; Duran et al., 2001) and prospective (Peppard et al., 2000). The Wisconsin Sleep Cohort study, a prospective study, tracked adults with sleep-disordered breathing for at least 4 years to determine new onset hypertension and other outcomes. The hypertensive effect was independent of obesity, age, gender, and other confounding factors. Controlling for obesity is especially important because it is a risk factor for hypertension as well as for OSA.

A causal association between OSA and hypertension is supported by evidence of a dose-response relationship; the higher the apnea-hypopnea index, the greater the increase in blood pressure (Peppard et al., 2000; Nieto

BOX 3-1

Definitions Impact Disease Prevalence Estimates

The metric used most commonly to define obstructive sleep apnea and to quantify its severity is the apnea-hypopnea index, derived by identifying and manually counting each respiratory disturbance (apnea and hypopnea) with subsequent division of the sum by the number of hours slept. Technology for measuring changes in airflow and ventilatory effort has evolved rapidly, with laboratories varying in the implementation of specific sensors and scoring approaches for identifying respiratory events. Variation in event identification has been particularly great for hypopneas (Moser et al., 1994), which requires identification of more subtle changes in airflow than do apneas, and often requires visualization of corroborative changes in oxygen desaturation or evidence of a cortical arousal. Variation in the sensors used to detect breathing changes, the amplitude criteria (from discernible to greater than 50 percent) applied to identify any given reductions in breathing signals as hypopneas, and different uses of corroborative data (associated desaturation and arousal) to discriminate “normal” from “hypopneic” breaths have all contributed to marked laboratory differences in events scored for clinical or research purposes. Likewise, there has been variation in the choice of threshold values for the apnea-hypopnea index considered to define the disease state. An analysis of over 5,000 records from the Sleep Heart Health Study underscores the potential variability introduced by varying either hypopnea definitions or threshold values. This analysis showed that the magnitude of the median apnea-hypopnea index varied 10-fold (i.e., 29.3 when the apnea-hypopnea index was based on events identified on the basis of flow or volume amplitude criteria alone to 2.0 for an apnea-hypopnea index that required an associated 5 percent desaturation with events) (Redline et al., 2000). Using any given definition but varying the threshold to define disease also resulted in marked differences in the percentage of subjects classified as diseased. For example, using an apnea-hypopnea index cutoff value of greater than 15 and an apnea-hypopnea index definition requiring a 5 percent level of desaturation resulted in a prevalence estimate of 10.8 percent. In contrast, almost the entire cohort was identified to be “affected” when sleep-disordered breathing was defined using an apnea-hypopnea index threshold of 5 and when all hypopneas were scored regardless of associated corroborative physiological changes. These data and others have identified the critical need for standardization. As such, at least three efforts led by professional organizations have attempted to develop standards. The latest efforts by the American Academy of Sleep Medicine (2005) have attempted to apply evidence-based guidelines to the recommendations. Unfortunately, the lack of prospective studies that allow various definitions to be compared relative to predictive ability have limited these initiatives, resulting in some recommendations reflecting consensus or expert opinion that may change as further research is developed.

et al., 2000). Both the Wisconsin Sleep Cohort study and the Sleep Heart Health Study showed dose-response relationships. The Sleep Heart Health Study is a community-based multicenter study of more than 6,000 middle-aged and older adults whose apnea-hypopnea index was measured by polysomnography. The likelihood of hypertension was greater at higher apnea-hypopnea index levels. Case-control studies reveal that approximately 30 percent of patients diagnosed with essential hypertension (hypertension in which the underlying cause cannot be determined) turn out to have sleep apnea (Partinen and Hublin, 2005). Further, evidence from pediatric studies indicate elevations in systemic blood pressure during both wakefulness and sleep in children with sleep apnea (Amin et al., 2004), with additional evidence of left ventricular wall changes by echocardiography.

The causal nature of the relationship between OSA and hypertension is reinforced by randomized controlled clinical trials showing that the most effective treatment for OSA, continuous positive airway pressure (CPAP) therapy, can reduce blood pressure levels. Although findings have been mixed in other studies, a critical review article that evaluated each study's methodology and results concluded that the trials show convincing decreases in blood pressure in those patients with severe OSA. The benefit is greatest in patients with severe OSA, determined by objective (polysomnography) and subjective (daytime sleepiness) criteria. The review also concluded that there was a lack of benefit in patients who had no daytime sleepiness (Robinson et al., 2004b). However, each of these studies was relatively small (less than 150 individuals), and findings can be considered only tentative.

How does OSA cause sustained hypertension? During the night, the apneas and hypopneas of OSA cause a transient rise in blood pressure (30 mm Hg or more) and increased activity of the sympathetic nervous system (Figure 3-5). Over time, the transient changes become more sustained and are detectable during the daytime, including evidence of sympathetic overactivity (Narkiewicz and Somers, 2003). Studies have found that people with OSA (versus those with similar blood pressure, but no OSA) have faster heart rates, blunted heart rate variability, and increased blood pressure variability—all of which are markers of heightened cardiovascular risk (Caples et al., 2005). The precise pathophysiological steps from transient vascular changes to systemic hypertension are far from clear but may involve oxidative stress, upregulation of vasoactive substances (Caples et al., 2005), and endothelial dysfunction (Faulx et al., 2004; Nieto et al., 2004; Young and Javaheri, 2005).

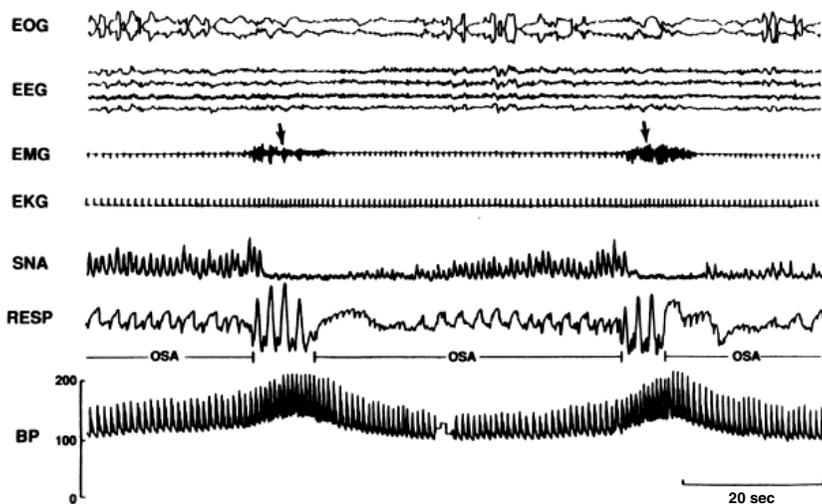


FIGURE 3-5 REM sleep recordings for an individual with OSA.

NOTE: During even the lowest phase, blood pressure during REM was higher than in the awake state. Electrooculogram (EOG), electroencephalogram (EEG), electromyogram (EMG), electrocardiogram (EKG), sympathetic nerve activity (SNA), respiration (RESP), blood pressure (BP).

SOURCE: Somers et al. (1995).

Obstructive Sleep Apnea Is Associated with Cardiovascular Disease and Stroke

Epidemiological studies reveal an association between OSA and cardiovascular disease, including arrhythmias (Guilleminault et al., 1983); coronary artery disease (Andreas et al., 1996) and specifically, myocardial infarction (Hung et al., 1990; D'Alessandro et al., 1990; Mooe et al., 1996a,b; Marin et al., 2005); and congestive heart failure (Javaheri et al., 1998). Most case-control studies detecting a relationship with myocardial infarction found adjusted odds ratios of around 4 (Young et al., 2002a,b). The large, cross-sectional Sleep Heart Health Study of nearly 6,500 (Shahar et al., 2001) found that participants in the highest apnea-hypopnea index quartile (index greater than 11) were 42 percent more likely to self-report cardiovascular disease (coronary heart disease, heart failure, or stroke) than those in the lowest quartile (adjusted OR = 1.42, 95% CI, 1.13–1.78). The adjusted OR for stroke was 1.58 (95% CI, 1.02–2.46). A higher probability of stroke associated with OSA is also supported by other studies (Bassetti and Aldrich, 1999; Parra et al., 2000; Yaggi et al., 2005; Bradley et al., 2005). In the Sleep Heart Health Study, apnea-hypopnea index was deter-

mined by polysomnography, and adjustments were made for a variety of confounding factors, including hypertension. That the hypertension adjustment did not eliminate the effect suggests that hypertension is not the exclusive means by which OSA may lead to cardiovascular disease. A limitation of cross-sectional and case-control analyses is that cause and effect cannot be determined: heart disease may have resulted in OSA or vice versa. However, an observational cohort study of 1,022 individuals, where 68 percent of individuals had OSA (apnea-hypopnea index of 5 or higher), showed that OSA syndrome significantly increased the risk of stroke or death from any cause, and the increase is independent of other risk factors, including hypertension (Yaggi et al., 2005). Other studies have confirmed the risk of OSA syndrome with stroke or death from any cause (Ayas et al., 2003; Gami et al., 2005). Furthermore, other large prospective studies also have shown an association between snoring—a marker for OSA—and incidence of cardiovascular diseases (Jennum et al., 1995; Hu et al., 2000), providing temporal associations in support of OSA playing a causal role in the development of heart diseases. As will be discussed in the next section, OSA is associated with glucose intolerance and diabetes, both of which are independent risk factors for cardiovascular disease.

Studies of the benefits of CPAP further support an association between cardiovascular disease and OSA. Marin and colleagues (2005), in a large, observational study of 10 years' duration, found that patients with untreated severe OSA (apnea-hypopnea index greater than 30), relative to those receiving CPAP treatment, with similar apnea-hypopnea index severity, had a higher incidence of fatal and nonfatal cardiovascular events. The events included myocardial infarction, stroke, and coronary artery bypass surgery. The untreated patients had refused CPAP but were followed regularly. A second study found an increased mortality rate from cardiovascular disease in individuals who did not maintain CPAP treatment over a 5-year follow-up period (Doherty et al., 2005). However, the number of new cases of cardiovascular disease was independent of CPAP treatment compliance. Although observational evidence of this type is not conclusive proof, because it may be subject to confounding by indication and other biases, it still lends weight to the strength of the association.

Most studies finding elevated cardiovascular disease risk have been conducted in adults. Whether or not children with sleep-disordered breathing are at risk for cardiovascular effects is not known. Children with OSA, as noted previously, do experience changes in blood pressure profiles, heart rate variability, and ventricular wall changes as measured by echocardiography (Marcus et al., 1998; Amin et al., 2005). The paucity of longitudinal data on OSA in children, in whom levels of OSA may vary during growth and development and in whom responses to therapies such as tonsillectomy may be variable (Morton et al., 2001), limits the ability to speculate on the

long-term cardiovascular effects of untreated sleep-disordered breathing in children. Nonetheless, evidence that as many as 20 to 25 percent of children may have persistent OSA even after tonsillectomy underscores the potential importance of OSA as an early childhood risk factor for later cardiovascular diseases (Amin et al., 2005; Larkin et al., 2005).

Obstructive Sleep Apnea Is Associated with Impaired Glucose Tolerance and Diabetes

OSA is associated with impaired glucose tolerance and insulin resistance, according data from several studies (Ip et al., 2002; Punjabi et al., 2002), including the Sleep Heart Health Study (Punjabi et al., 2004). Those outcomes were more prevalent in those with the highest apnea-hypopnea index. The study also found a relationship between sleep-related hypoxemia and glucose intolerance, which has implications for understanding mechanisms behind the OSA-glucose intolerance link (see below). The Sleep Heart Health Study, as noted earlier, was a large, cross-sectional, community-based study that used polysomnography to identify OSA. The analyses adjusted for obesity (BMI and waist circumference), self-reported sleep duration, and other confounding factors. The findings suggest that OSA contributes to the onset of diabetes through the development of glucose intolerance and insulin resistance, which are established pathophysiological processes in diabetes (Martin et al., 1992).

Of studies that have examined diabetes as an outcome measure, the largest was the prospective Nurses' Health Study. The study found that, after 10 years of follow-up, occasional snoring (versus nonsnoring) was associated with an elevated risk of new onset diabetes in women, and the risk was even greater for regular snoring (Al-Delaimy et al., 2002). Regular or habitual snoring is an indicator of OSA.

The relationship between OSA and metabolic changes that may lead to diabetes is reinforced by studies of the benefits of CPAP. CPAP alleviates glucose intolerance in the short term and long term (Brooks et al., 1994; Harsch et al., 2004). In a separate study of people with type 2 diabetes as well as OSA, CPAP improved glycemic control (Babu et al., 2005). Recent data also indicate that diabetics with OSA have poorer control of glucose levels, with improvement following treatment of OSA with CPAP (Babu et al., 2005).

The mechanisms by which OSA disrupts glucose metabolism are not established. Drawing on human studies and animal models, the biochemical cascade begins with intermittent hypoxia and recurrent sleep arousals (sleep fragmentation). These events stimulate the sympathetic nervous system, hypothalamic-pituitary-adrenal axis, and adipocytes (Punjabi and Beamer, 2005). Their activation, in turn, leads to release of catecholamines, cortisol, and inflammatory cytokines and other vasoactive intermediates,

which may mediate the development of glucose intolerance, insulin resistance, and, ultimately, type 2 diabetes. Because diabetes is also a risk factor for cardiovascular disease, the interrelationships may partly explain why OSA predisposes to cardiovascular disease (Punjabi and Beamer, 2005).

Obstructive Sleep Apnea May Contribute to Obesity

Up to 40 percent of people who are morbidly obese have OSA (Vgontzas et al., 1994). This finding may reflect the role of obesity as a well-established risk factor for the development of OSA. It may also reflect obesity as a *consequence* of OSA, although the evidence is not yet conclusive (Grunstein, 2005b). Patients with newly diagnosed OSA, compared with controls matched for BMI and percent body fat, show recent weight gain (Phillips et al., 1999). Data from the Wisconsin Sleep Cohort also show that individuals with OSA have reduced levels of physical activity; OSA-related sleepiness may contribute to changes in activity and energy expenditure, and thus contribute to weight gain. OSA-related hormonal changes may also contribute to obesity. In general, patients with OSA have higher levels of leptin, the appetite-suppressing hormone (Phillips et al., 2000; Palmer et al., 2004; Patel et al., 2004) than controls. However, their morning levels are relatively lower than evening levels (Patel et al., 2004). Thus, either via leptin resistance (where high levels of leptin are present, but tissues are poorly responsive to leptin's action) or because of disturbances in diurnal variability in leptin, individuals with OSA may be predisposed to lower effective levels of appetite suppressing hormones. Although CPAP reduces leptin levels, it is not known whether such effects relate to differences in the effectiveness of leptin's actions (Chin et al., 2003). Furthermore, obesity also affects the severity of OSA. Significant weight loss in adolescents who underwent gastric bypass surgery (mean, 58 kg) was associated with a dramatic reduction of OSA severity (Kalra et al., 2005).

Etiology and Risk Factors

In simplest terms, OSA is caused by narrowing or collapse of the airway as a result of anatomical and physiological abnormalities in pharyngeal structures. Apnea episodes cause hypoxemia (insufficient oxygen in the blood) and hypercapnia (high concentration of blood carbon dioxide). The episodes also increase the output of the sympathetic nervous system (Narkiewicz and Somers, 2003), the effect of which is to restore pharyngeal muscle tone and reopen the airway. Although increased sympathetic activity is beneficial for restoring normal breathing and oxygen intake over the short term, it has long-term deleterious effects on vascular tone and blood pressure, among other effects (Caples et al., 2005). These early events—which are

mediated by a variety of chemoreceptors in the carotid body and brainstem—trigger pathophysiological changes that occur not only during the obstructive apneas, but also extend into wakeful states during the day. For example, during daytime wakefulness, people with OSA have higher sympathetic activity (Somers, et al., 1995) and heightened chemoreflex sensitivity, which in turn generates an increased ventilatory response (Narkiewicz et al., 1999). The full pathophysiology of OSA remains somewhat elusive, although research is piecing together the relationships between OSA and a range of the previously described long-term health effects. The etiology of central sleep apnea, although also not well understood, is hypothesized to result from instability of respiratory control centers (White, 2005).

There are a number of risk factors for OSA, including:

- Obesity, male gender, and increasing age (Table 3-1) (Young et al., 1993). It is unclear how incidence changes with older age; some data suggest that snoring and OSA may decline after age 65 years (Young et al., 1993); however, other studies show very high prevalence rates of OSA in elderly individuals (Bliwise et al., 1988; Ancoli-Israel et al., 1993; Foley et al., 2003). The pathophysiological roles of these risk factors are not well understood, although evidence suggests that fat deposition in the upper airways, which is more likely in males, contributes to the physical narrow-

TABLE 3-1 Risk Factors for Obstructive Sleep Apnea

Risk Factor	Reference
Obesity and BMI greater than 25 kg/m ²	Grunstein et al., 1993
Male gender	Strohl and Redline, 1996; Kapsimalis and Kryger, 2002; Sheperdycky et al., 2005
Familial association	Guilleminault et al., 1995; Pillar and Lavie, 1995; Redline et al., 1995; Buxbaum et al., 2002
Alcohol consumption	Taasan et al., 1981
Cranial facial structure High and narrow hard palate, elongated soft palate, small chin, and abnormal overjet	Ferguson et al., 1995
Enlargement of the tonsils	Behlfelt, 1990
Lesions of the autonomic nervous system	Mondini and Guilleminault, 1985; Rosen et al., 2003
Race: African Americans, Mexican Americans, Pacific Islanders, and East Asians	Schmidt-Nowara et al., 1990; Redline et al., 1997; Li et al., 2000

ing that causes OSA (Robinson et al., 2004a). Menopause also increases the risk of OSA (Bixler et al., 2001; Young et al., 2003), possibly through lower levels of progesterone hormones that influence the respiratory system through changes in body fat distribution (Vgontzas and Kales, 1999). However, recent studies suggest that there may be a referral bias that results in a lower apparent rate of sleep apnea in females than in males (Kapsimalis and Kryger, 2002; Sheperdycky et al., 2005). Epidemiological evidence suggests that hormone replacement therapy lessens the risk of OSA (Shahar et al., 2003). In children, the main risk factor for OSA is tonsillar hypertrophy, although OSA may also occur in children with congenital and neuromuscular disorders and in children who were born prematurely (Rosen et al., 2003). Asthma, a common childhood respiratory illness, is also associated with OSA in children (Sulit et al., 2005).

- In adolescents, risk factors may be more similar to those seen in adults and include obesity (Redline et al., 1999). Being a minority is a risk factor for both increased prevalence and severity of sleep-disordered breathing in both children and adults (Rosen et al., 1992; Ancoli-Israel et al., 1995; Rosen et al., 2003). The prevalence of sleep-disordered breathing in the United States is approximately three times higher in middle-aged members of minority groups compared to non-Hispanic whites (Kripke et al., 1997). African American children are at increased risk, even after adjusting for obesity or respiratory problems (Redline et al., 1999; Rosen et al., 2003). Familial and probably genetic factors strongly contribute to OSA (Buxbaum et al., 2002; Palmer LJ et al., 2003; Palmer et al., 2004).

- Patients with cardiovascular disease and diabetes are also at higher risk for developing both OSA and central sleep apnea (Sin et al., 1999).

- Patients with impaired baroreflexes (e.g., patients with hypertension or heart failure and premature infants) may be especially susceptible to excessive autonomic responses to chemoreflex stimulation during periods of apnea. In these patient groups, bradyarrhythmias, hypoxia, hypoperfusion, and sympathetic activation during apnea may predispose to sudden death (Somers et al., 1988; 1992).

Sleep-Disordered Breathing May Affect Mortality

Limited evidence suggests that sleep-disordered breathing may affect an individual's mortality (Young et al., 2002a,b; Lavie et al., 2005). Studies of patients at sleep clinics tend to show an association between sleep apnea and mortality (He et al., 1988), but several well-designed, population-based studies failed to find an association (Ancoli-Israel et al., 1996; Lindberg et al., 1998; Kripke et al., 2002), except in one subgroup of patients below age 60 with both snoring and excessive daytime sleepiness. The subgroup experienced twice the risk of mortality (Lindberg et al., 1998). A recent observa-

tional study of a large cohort of sleep apnea patients ($n = 403$), snorers, and healthy controls who had been followed for an average of 10 years, found a threefold higher risk of fatal cardiovascular events with severe OSA (Marin et al., 2005). An observational follow-up study of the long-term effects of CPAP therapy on mortality found that compared to individuals that began receiving CPAP therapy for at least 5 years ($n = 107$), individuals that were untreated with CPAP ($n = 61$) were more likely to die from cardiovascular disease (14.8 percent versus 1.9 percent, log rank test, $P = .009$) (Yaggi et al., 2005; Doherty et al., 2005).

Treatment

In adults, OSA is most effectively treated with CPAP and weight loss (Strollo et al., 2005; Grunstein, 2005a). Evidence of CPAP's efficacy for alleviating daytime sleepiness comes from randomized controlled trials and meta-analysis (Patel et al., 2003). The problem is that many patients are noncompliant with CPAP (see Chapter 6). Other options, although less effective, include a variety of dental appliances (Ferguson and Lowe, 2005) or surgery (e.g., uvulopalatopharyngoplasty) (Powell et al., 2005). In children, the first-line treatment for most cases of OSA is adenotonsillectomy, according to clinical practice guidelines developed by the American Academy of Pediatrics (Marcus et al., 2002). Children who are not good candidates for this procedure can benefit from CPAP. Central apnea treatment is tailored to the cause of the ventilatory instability. Commonly used treatments include oxygen, CPAP, and acetazolamide, a drug that acts as a respiratory stimulant (White, 2005).

INSOMNIA

Manifestations and Prevalence

Insomnia is the most commonly reported sleep problem (Ohayon, 2002). It is a highly prevalent disorder that often goes unrecognized and untreated despite its adverse impact on health and quality of life (Benca, 2005a) (see also Chapter 4). Insomnia is defined by having difficulty falling asleep, maintaining sleep, or by short sleep duration, despite adequate opportunity for a full night's sleep. Other insomnia symptoms include daytime consequences, such as tiredness, lack of energy, difficulty concentrating, and/or irritability (Simon and VonKorff, 1997). The diagnostic criteria for primary insomnia include:

- Difficulty initiating or maintaining sleep or nonrestorative sleep.

- Causing clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- Not occurring exclusively during the course of another sleep disorder.
- Not due to the direct physiological effects of a substance or a medical condition (APA, 1994).

Insomnia symptoms are remarkably common, affecting at least 10 percent of adults in the United States (Ford and Kamerow, 1989; Ohayon et al., 1997; Simon and VonKorff, 1997; Roth and Ancoli-Israel, 1999). Prevalence is higher among women and older individuals (Mellinger et al., 1985; Ford and Kamerow, 1989; Foley et al., 1995). Severe insomnia tends to be chronic, with about 85 percent of patients continuing to report the same symptoms and impairment months or years after diagnosis (Hohagen et al., 1993; Katz and McHorney, 1998). The comorbidity of sleep disorders with psychiatric disorders is covered later in this chapter.

Etiology and Risk Factors

The precise causes of insomnia are poorly understood but, in general terms, involve a combination of biological, psychological, and social factors. Insomnia is conceptualized as a state of hyperarousal (Perlis et al., 2005). Stress is thought to play a leading role in activating the hypothalamic-pituitary axis and setting the stage for chronic insomnia. A key study showed that adults with insomnia, compared with normal sleepers, have higher levels, over a 24-hr period, of cortisol and adrenocorticotropic hormone (ACTH), which are hormones released by the hypothalamic-pituitary-adrenal axis after stress exposure (Vgontzas et al., 2001). The 24-hour pattern of cortisol and ACTH secretion is different, however, from that in individuals who are chronically stressed. Cognitive factors, such as worry, rumination, and fear of sleeplessness, perpetuate the problem through behavioral conditioning. Other perpetuating factors include light exposure and unstable sleep schedules (Partinen and Hublin, 2005).

Insomnia patients often attribute their difficulty sleeping to an overactive brain. Several lines of evidence, from preclinical to sleep neuroimaging studies in insomnia patients, suggest that there are multiple neural systems arranged hierarchically in the central nervous system that contribute to arousal as well as insomnia complaints. Disturbances in these systems may differ according to the nature of insomnia. Structures that regulate sleep and wakefulness, for example the brainstem, hypothalamus and basal forebrain, are abnormally overactive during sleep in primary insomnia patients (Nofzinger et al., 2004b). In addition, limbic and paralimbic structures that regulate basic emotions and instinctual behaviors such as the amygdala, hippocampus, ventromedial prefrontal cortex and anterior cingulate cortex

have been shown to be abnormally active during sleep in individuals with primary insomnia and secondary insomnias related to depression (Nofzinger et al., 2004a, 2005). Abnormal activity in neocortical structures that control executive function and are responsible for modulating behavior related to basic arousal and emotions has been observed in individuals with insomnias associated with depression (Nofzinger et al., 2004a, 2005).

The two main risk factors of insomnia are older age and female gender (Edinger and Means, 2005). One large, population-based study found that insomnia was nearly twice as common in women than men, although reporting bias cannot be ruled out as a contributing factor (Ford and Kamerow, 1989). The reason behind the apparent higher prevalence in women is not understood. Other risk factors for insomnia include family history of insomnia (Dauvilliers et al., 2005), stressful life styles, medical and psychiatric disorders, and shift work (Edinger and Means, 2005). Although adolescent age is not viewed a risk factor, insomnia has rarely been studied in this age group.

Treatment

Insomnia is treatable with a variety of behavioral and pharmacological therapies, which may be used alone or in combination. While the therapies currently available to treat insomnia may provide benefit, the 2005 NIH State of the Science Conference on the Manifestations and Management of Chronic Insomnia concluded that more research and randomized clinical trials are needed to further verify their efficacy, particularly for long-term illness management and prevention of complications like depression (NIH, 2005). Behavioral therapies appear as effective as pharmacological therapies (Smith et al., 2002), and they may have more enduring effects after cessation (McClusky et al., 1991; Hauri, 1997). Behavioral therapies, according to a task force review of 48 clinical trials, benefit about 70 to 80 percent of patients for at least 6 months after completion of treatment (Morin et al., 1999; Morin, 2005). The therapies are of several main types (Table 3-2). The major problem with current behavioral therapies is not their efficacy; rather it is lack of clinician awareness of their efficacy and lack of providers sufficiently trained and skilled in their use. Other problems are their cost and patient adherence (Benca, 2005a). A specific strategy to improve an individual's sleep quality is by promoting proper sleep hygiene (Kleitman, 1987; Harvey, 2000).

The most efficacious pharmacological therapies for insomnia are hypnotic agents of two general types, benzodiazepine or nonbenzodiazepine hypnotics (Nowell et al., 1997). Nonbenzodiazepine hypnotics are advantageous because they generally have shorter half-lives, thus producing fewer impairments the next day, but the trade-off is that they may not be as effective at

TABLE 3-2 Psychological and Behavioral Treatments for Insomnia

Therapy	Description
Stimulus control therapy	A set of instructions designed to reassociate the bed/bedroom with sleep and to reestablish a consistent sleep-wake schedule: Go to bed only when sleepy; get out of bed when unable to sleep; use the bed/bedroom for sleep only (e.g., no reading, watching TV); arise at the same time every morning; no napping.
Sleep restriction therapy	A method to curtail time in bed to the actual sleep time, thereby creating mild sleep deprivation, which results in more consolidated and more efficient sleep.
Relaxation training	Clinical procedures aimed at reducing somatic tension (e.g., progressive muscle relaxation, autogenic training) or intrusive thoughts (e.g., imagery training, meditation) interfering with sleep.
Cognitive therapy	Psychotherapeutic method aimed at changing faulty beliefs and attitudes about sleep, insomnia, and the next-day consequences. Other cognitive strategies are used to control intrusive thoughts at bedtime and prevent excessive monitoring of the daytime consequences of insomnia.
Sleep hygiene education	General guidelines about health practices (e.g., diet, exercise, substance use) and environmental factors (e.g., light, noise, temperature) that may promote or interfere with sleep.

SOURCE: Morin (2005).

maintaining sleep throughout the night (Morin, 2005; Benca, 2005a). It is still unclear whether hypnotics lead to dependence. It is suggested that they should not be taken for more than 10 days in a row; however, recent studies suggest that hypnotics do not always lead to dependence (Hajak et al., 2003; Walsh et al., 2005; Benca, 2005a). There have been no large-scale trials examining the safety and efficacy of hypnotics in children and adolescents. Other pharmacological classes used for insomnia include sedating antidepressants, antihistamines, and antipsychotics, but their efficacy and safety for treating insomnia have not been thoroughly studied (Walsh et al., 2005).

SLEEP AND PSYCHIATRIC DISORDERS

Manifestations and Prevalence

Sleep disturbances are common features of psychiatric disorders. The most frequent types of sleep disturbances are insomnia, excessive daytime

sleepiness (hypersomnia), and parasomnia. Sleep disturbances are so commonly seen as symptoms of certain psychiatric disorders that they are listed as diagnostic criteria under DSM-IV (APA, 1994). For example, insomnia is a symptom used with others to diagnose major depression. The comorbidity, or coexistence, of a full-blown sleep disorder (particularly insomnia and hypersomnia) with a psychiatric disorder is also common. Forty percent of those diagnosed with insomnia, in a population-based study, also have a psychiatric disorder (Ford and Kamerow, 1989). Among those diagnosed with hypersomnia, the prevalence of a psychiatric disorder is somewhat higher—46.5 percent.

The reasons behind the comorbidity of sleep and psychiatric disorders are not well understood. Comorbidity might be due to one disorder being a risk factor or cause of the other; they might both be manifestations of the same or overlapping physiological disturbance; one might be a consequence of the other. In some cases, the sleep disturbance can be both cause and consequence. In generalized anxiety disorder, for example, the symptoms of fatigue and irritability used to diagnose it are often the result of a sleep disturbance, which itself is also a diagnostic symptom.

Adolescents with major depressive disorders report higher rates of sleep problems and, conversely, those with sleep difficulties report increased negative mood or mood regulation (Ryan et al., 1987). In addition, sleep-onset abnormalities during adolescence have been associated with an increased risk of depression in later life (Rao et al., 1996).

The best studied and most prevalent comorbidity is insomnia with major depression. Insomnia as a symptom of depression is highly common. On the basis of longitudinal studies, insomnia is now established as a risk factor for major depression. Not all people with insomnia have a depression diagnosis; however, studies have found that 15 to 20 percent of people diagnosed with insomnia have major depression (Ford and Kamerow, 1989; Breslau et al., 1996).

Depressed individuals have certain abnormalities detected by polysomnography. One is shorter rapid eye movement (REM) latency (a shorter period of time elapsing from onset of sleep to onset of REM sleep), an effect that persists even after treatment for depression. Other abnormalities include shortened initial REM period, increased REM density, and slow-wave deficits (Benca, 2005a). Shorter REM latency and slow-wave sleep (SWS) deficits tend to run in families; these abnormalities are also found in first-degree relatives of people with major depression, but who are unaffected by depression (Giles et al., 1998). A variety of polysomnographic abnormalities have been found with other psychiatric disorders (Benca, 2005a).

Etiology and Risk Factors

The etiological basis for the comorbidity of sleep disorders and psychiatric disorders is not well understood. Most potential mechanisms for sleep changes in psychiatric disorders deal specifically with insomnia and depression. Possible mechanisms include neurotransmitter imbalance (cholinergic-aminergic imbalance), circadian phase advance, and hypothalamic-pituitary-adrenal axis dysregulation (Benca, 2005a). Recent evidence implicating regions of the frontal lobe has emerged from imaging studies using positron emission tomography. As they progress from waking to non-REM (NREM) sleep, depressed subjects have smaller decreases in relative metabolism in regions of the frontal, parietal, and temporal cortex when compared to individuals who are healthy (Nofzinger et al., 2005). Normally, the transition from waking to NREM sleep is associated with decreases in these frontal lobe regions. What appears to occur with depression is that the decrease is less pronounced. Another finding of the study is that during both waking and NREM sleep, depressed patients show hypermetabolism in the brain's emotional pathways, including the amygdala, anterior cingulate cortex, and related structures. Because the amygdala also plays a role in sleep regulation (Jones, 2005), this finding suggests that sleep and mood disorders may be manifestations of dysregulation in overlapping neurocircuits. The authors hypothesize that increased metabolism in emotional pathways with depression may increase emotional arousal and thereby adversely affect sleep (Nofzinger et al., 2005).

Treatment

Comorbid psychiatric and sleep disorders are treated by a combination of medication and/or psychotherapy (Krahn, 2005; Benca, 2005a). A major problem is underdiagnosis and undertreatment of one or both of the comorbid disorders. One of the disorders may be missed or may be mistakenly dismissed as a condition that will recede once the other is treated. In the case of depression, for example, sleep abnormalities may continue once the depression episode has remitted (Fava, 2004). If untreated, residual insomnia is a risk factor for depression recurrence (Reynolds et al., 1997; Ohayon and Roth, 2003). Further, because sleep and psychiatric disorders, by themselves, are disabling, the treatment of the comorbidity may reduce needless disability. Insomnia, for example, worsens outcomes in depression, schizophrenia, and alcohol dependence. Treatment of both conditions can improve a patient's functioning and possibly improve adherence with therapy (Vincent and Hameed, 2003). Another concern is that medication for one disorder might exacerbate the other (e.g., prescription of sedating antidepressants for patients with hypersomnolence). The choice of medica-

tion for psychiatric disorder (or vice versa) should be influenced by the nature of the sleep complaint (e.g., more sedating antidepressant taken at night for insomnia; more alerting antidepressant for excessive daytime sleepiness).

Insomnia and Psychiatric Disorders

As mentioned above insomnia is associated with depression, acting as both a risk factor and a manifestation (Ford and Kamerow, 1989; Livingston et al., 1993; Breslau et al., 1996; Weissman et al., 1997; Chang et al., 1997; Ohayon and Roth, 2003; Cole and Dendukuri, 2003). Several studies done were longitudinal in design, including one that tracked more than 1,000 male physicians for 40 years (Chang et al., 1997). Another study, which followed 1,007 young adults at a health maintenance organization for 3.5 years, found that a history of insomnia at baseline not only predicted new onset depression, but also other psychiatric disorders (any anxiety disorder, alcohol abuse, drug abuse, and nicotine dependence) (Breslau et al., 1996) (Figure 3-6). The adjusted odds of developing a psychiatric disorder were highest for depression (OR = 3.95; 95% CI, 2.2–7.0). This figure is based on 16 percent of the sample who developed depression with a history of insomnia at baseline, as compared with 4.6 percent who developed depression without a history of insomnia. The study's general findings

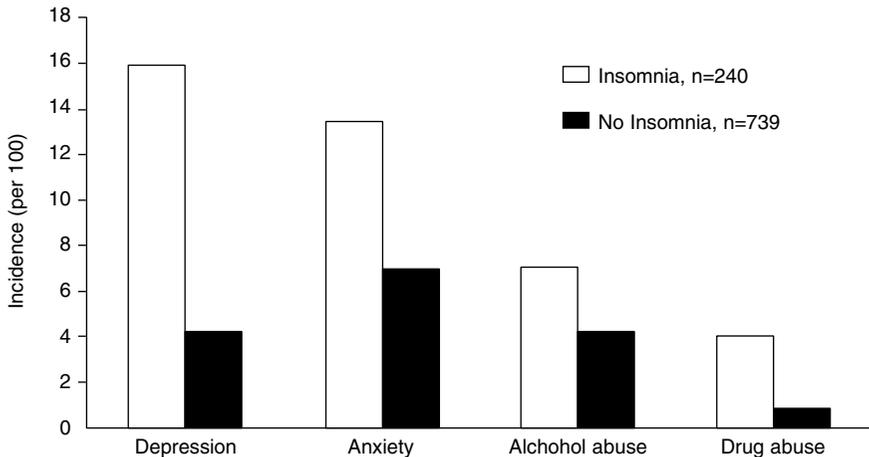


FIGURE 3-6 Incidence of psychiatric disorders during 3.5 years of follow-up of patients with a prior history of insomnia.
SOURCE: Breslau et al. (1996).

are supported by another large study of 10,000 adults by Weissman and colleagues (1997). That study found insomnia to have increased the risk of major depression by a similar magnitude (fivefold) and to have increased the risk of panic disorder (one of the anxiety disorders) even more strikingly, by 20-fold (OR = 20.3, 95% CI, 4.4–93.8). Insomnia is also a predictor of acute suicide among patients with mood disorders (Fawcett et al., 1990).

The striking association between insomnia and depression in so many studies suggests that insomnia is also an early marker for the onset of depression, and the two may be linked by a common pathophysiology. Although the pathophysiological relationship is not known, researchers are focusing on overlapping neural pathways for anxiety, arousal, and/or circadian disturbance (Benca, 2005b). One hypothesis is that common pathways are the amygdala and other limbic structures of the brain (Nofzinger et al., 2005). Another hypothesis is that chronic insomnia increases activity of the hypothalamic-pituitary-adrenal axis, which in turn contributes to depression (Perlis et al., 2005). The close association of insomnia and depression also raises the tantalizing possibility that treating insomnia may prevent some cases of depression (Riemann and Voderholzer, 2003), but limited data are available. The biological basis for the relationship between insomnia and new onset psychiatric disorders (other than depression) is also not known.

NARCOLEPSY AND HYPERSOMNIA

Manifestations and Prevalence

Narcolepsy and idiopathic hypersomnia are characterized by a clinically significant complaint of excessive daytime sleepiness that is neither explained by a circadian sleep disorder, sleep-disordered breathing, or sleep deprivation, nor is it caused by a medical condition disturbing sleep (AASM, 2005). The diagnosis of narcolepsy and hypersomnia is based principally on the Multiple Sleep Latency Test (MSLT), which objectively quantifies daytime sleepiness (Box 3-2) (Carskadon et al., 1986; Arand et al., 2005). Sleep logs or actigraphy (a movement detector coupled with software that uses movement patterns to provide estimate sleep and wake times) can also be used to exclude chronic sleep deprivation as a diagnosis prior to the MSLT. In many cases narcolepsy arises during the mid to late teenage years; however, frequently initial diagnosis is not correct, resulting in delays in diagnosis of 15 to 25 years after the onset of symptoms (Broughton et al., 1997). Onset of narcolepsy can also have a negative impact on school performance (see Chapter 4). Narcolepsy is associated with a number of symptoms (Anic-Labat et al., 1999; Overeem et al., 2002), including the following:

- Excessive daytime sleepiness, defined as a background of constant sleepiness with sleep attacks leading to unintended napping during the day. In most cases, naps are refreshing, but the rested feeling only lasts a short time. When severe, sleepiness can manifest as automatic behavior, a continuation of activities in a semiautomatic manner when sleepy, with no subsequent memory.
- Cataplexy, which are sudden and brief bilateral episodes of muscle weakness triggered by a strong emotional stimulus, such as laughing.

BOX 3-2

Clinical Laboratory Findings in Narcolepsy and Hypersomnia

The Multiple Sleep Latency Test (MSLT) objectively quantifies daytime sleepiness. It consists of five 20 minute daytime naps at 2-hour intervals. The amount of time it takes to fall asleep (sleep latency) and the occurrence of rapid eye movement (REM) sleep is recorded. Mean sleep latency of less than 8 minutes and two or more sleep onset rhythmic eye movement periods is diagnostic for narcolepsy. The MSLT must always be preceded by nocturnal sleep polysomnography to rule out other causes of short MSL or sleep onset rhythmic eye movement periods such as OSA, insufficient sleep, or delayed sleep phase syndrome. At least 6 hours of sleep must have occurred prior to the MSLT. Sleep logs or actigraphy for the preceding 2 weeks can be helpful to exclude chronic sleep deprivation. It must also be conducted after withdrawal of psychotropic medications (generally more than 2 weeks). Antidepressants, most notably, suppress REM sleep and/or may create REM rebound if stopped too recently prior to testing.

HLA-DQB1*0602 is the human leukocyte antigen DQB1 subtype associated with narcolepsy. Almost all cases with cataplexy are DQB1*0602 positive; approximately 40 percent of narcolepsy cases without cataplexy are HLA-DQB1*0602 positive. The test is not highly predictive of narcolepsy, however, as 25 percent of the population is HLA-DQB1*0602 positive. Idiopathic and recurrent hypersomnia cases are not strongly associated with human leukocyte antigen.

Cerebrospinal fluid (CSF) hypocretin-1, also called orexin-A, is a neuropeptide involved in the cause of narcolepsy and cataplexy. It can be measured in the CSF, and this has been used to diagnose narcolepsy. Most cases with cataplexy (and HLA-DQB1*0602) have CSF hypocretin-1 levels below 30 percent of normal control value. This finding is very specific and sensitive for narcolepsy and cataplexy. Low CSF hypocretin is also diagnostic of narcolepsy without cataplexy, but is found in only a small portion of these cases (7 to 40 percent).

- Sleep paralysis, or muscle paralysis akin to REM sleep atonia while awake, when falling asleep, or waking up.
- Hypnagogic/hypnopompic hallucinations, which are dreamlike REM sleep experiences, often frightening, that occur when falling asleep or waking up.
- Insomnia, typically difficulty maintaining sleep.
- Autonomic behavior, or continue to function (talking, putting things away, etc.) during sleep episodes but awakens with no memory of performing such activities.
- REM behavior disorder, characterized by excessive motor activity during REM sleep (Anic-Labat et al., 1999; Overeem et al., 2002).

Narcolepsy can be diagnosed clinically, by using the MSLT, or by measuring cerebrospinal fluid (CSF) hypocretin-1 (Box 3-2).

Idiopathic hypersomnia is classically separated into two subtypes. The first, idiopathic hypersomnia with prolonged sleep time, is a rare disorder and is characterized by the following:

- Excessive daytime sleepiness occurs, as described above for narcolepsy, but in the typical form naps are unrefreshing.
- Excessive amounts of daily sleep, typically defined as more than 10 hours of sleep per day, as documented for long periods of time using daily logs and sleep studies.
- Sleep drunkenness (sometimes referred to as sleep inertia)—difficulty waking up and individual is foggy for long periods of time after wake onset.

The second subtype of idiopathic hypersomnia, idiopathic hypersomnia without long sleep time, is characterized by a complaint of excessive daytime sleepiness and a short mean sleep latency on the MSLT.

In most sleep disorders clinics with experience in this area, approximately one-third of hypersomnia cases are diagnosed with this condition (Aldrich, 1996). The prevalence is estimated to be around 0.01 percent. In contrast, the prevalence of idiopathic hypersomnia without prolonged sleep time may be more substantial, as most patients are likely not diagnosed (Arand et al., 2005).

Recurrent hypersomnia is periodic either in synchrony with menstruation (menstruation-linked periodic hypersomnia) or without any association and mostly in males with Klein-Levin syndrome (Billiard and Cadilhac, 1988; Arnulf et al., 2005a). Klein-Levin syndrome is characterized by recurrent episodes of dramatic hypersomnia lasting from 2 days to several weeks. These episodes are associated with behavioral and cognitive abnormalities, binge eating or hypersexuality, and alternate with long asymptomatic periods that last months or years (Arnulf et al., 2005a).

Narcolepsy and hypersomnia can affect children, adolescents, adults, and older persons. In most cases these disorders begin in adolescence. The prevalence of narcolepsy with definite cataplexy has been documented in adults by numerous population-based studies and occurs in 0.02 to 0.05 percent of the population of Western Europe and North America (Mignot, 1998). In contrast, very little is known about the prevalence of narcolepsy without cataplexy. Recent studies using the MSLT indicate that approximately 3.9 percent of the general population has MSLT score abnormalities consistent with narcolepsy without cataplexy (Singh et al., 2005).

Secondary cases of narcolepsy or hypersomnia are also common, but the overall prevalence is not known (Table 3-3). These can occur in the context of psychiatric disorders, for example depression; central nervous system tumors, most notably in the hypothalamus; neurodegenerative disorders, such as Parkinson's disease; inflammatory disorders, such as multiple sclerosis or paraneoplastic syndromes; traumatic disorders, such as head trauma; vascular disorders, such as those that are attributed to median thalamic stroke; and genetic disorders, including myotonic dystrophy or Prader-Willi syndrome (Billiard et al., 1994; Mignot et al., 2002a).

Etiology and Risk Factors

Similar to other sleep disorders, little is known about the pathophysiology and risk factors for narcolepsy and hypersomnia. Most of the knowledge in this area pertains to narcolepsy with cataplexy, which affects males and females equally. Symptoms usually arise during adolescence. Many contributing factors influence an individual's susceptibility, including both genetic and environmental factors (Mignot, 1998, 2001).

Virtually all individuals who suffer narcolepsy with cataplexy carry the haplotype HLA-DQB1*0602 and have severe neuronal loss in regions of the brain that are responsible for regulating the sleep-wake cycle. Approximately 70,000 hypothalamic neurons that are responsible for producing the neuropeptide hypocretin (orexin) are lost in individuals with narcolepsy with cataplexy (Thannickal et al., 2000; Peyron et al., 2000). Hypocretin is an excitatory neuropeptide that regulates the activity of other sleep regulatory networks. Consequently, in some cases low levels of hypocretin-1 in the CSF, may be used to diagnose narcolepsy (Kanbayashi et al., 2002; Krahn et al., 2002; Mignot et al., 2002a) (Table 3-3). The cause of hypocretin cell loss is unknown but it may be autoimmune due to the association with the HLA-DQB1*0602 (Juji et al., 1984; Mignot, 2001).

Less is known regarding the pathophysiology of narcolepsy without cataplexy. The etiology is likely heterogeneous. An unknown portion may be caused by partial or complete hypocretin deficiency (Kanbayashi et al., 2002; Krahn et al., 2002; Mignot et al., 2002a). However, it has been

TABLE 3-3 International Classification of Sleep Disorders: Definitions, Prevalence, and Pathophysiology of Narcolepsy and Hypersomnias

Condition	Diagnostic Criteria	North American Prevalence	Pathophysiology and Etiology
Narcolepsy with cataplexy	Presence of definite cataplexy; usually abnormal MSLT results	0.02–0.18%	Hypocretin deficiency; 90% with low CSF HCRT-1 and positive for HLA-DQB1*0602
Narcolepsy without cataplexy	MSLT: mean sleep latency less than or equal to 8 minutes, 2 or greater SOREMPs; no or doubtful cataplexy	0.02%; many undiagnosed	Unknown, probably heterogeneous; 7–25% with low CSF HCRT-1, 40% HLA-DQB1*0602 positive
Secondary narcolepsy or hypersomnia	As above, but due to other known medical conditions (e.g., neurological)	Unknown	With or without hypocretin deficiency
Idiopathic hypersomnia with prolonged sleep	MSLT: short mean sleep latency, greater than two SOREMPs; long (10 hours or greater) unrefreshing nocturnal sleep	Rare, maybe 0.01–0.02%	Unknown, probable heterogeneous etiology
Idiopathic hypersomnia with normal sleep length	MSLT: short mean sleep latency, less than two SOREMPs; normal nightly sleep amounts (less than 10 hours)	Probably common, unknown prevalence	Unknown, probable heterogeneous etiology
Periodic hypersomnia (includes Kleine-Levin syndrome)	Recurrent (more than 1 time per year) sleepiness (lasting 2 to 28 days), normal function between occurrences	Rare, probably less than one per one million people	Unknown, probable heterogeneous etiology

NOTE: CSF, lumbar sac cerebrospinal fluid; HCRT, hypocretin; HLA, human leukocyte antigen; MSLT, Multiple Sleep Latency Test; SOREMP, sleep-onset REM period.

SOURCE: AASM (2005).

hypothesized that some individuals with partial cell loss may have normal CSF hypocretin-1 (Mignot et al., 2002a; Scammell, 2003).

The pathophysiology of idiopathic hypersomnia is unknown. When the disorder is associated with prolonged sleep time, it typically starts during adolescence and is lifelong. It is essential to exclude secondary causes, such as head trauma or hypersomnia owing to depression (Roth, 1976; Billiard and Dauvilliers, 2001). Some cases with prolonged sleep times have been reported to be familial, suggesting a genetic origin. Even less is known about idiopathic hypersomnia with normal sleep time. This condition is more variable and symptomatically defined. The cause of Kleine-Levin syndrome is unknown (Arnulf et al., 2005b).

Treatment

Treatment for these conditions is symptomatically based. Even in the case of narcolepsy in which the disorder is caused by hypocretin deficiency, current treatment does not aim at improving the defective neurotransmission (Mignot et al., 1993; Nishino and Mignot, 1997; Wisor et al., 2001). Behavioral measures, such as napping, support groups, and work arrangements are helpful but rarely sufficient. In most cases, pharmacological treatment is needed (Nishino and Mignot, 1997; Lammers and Overeem, 2003). However, as with other pharmaceuticals designed to treat sleep problems, large-scale clinical trials have not examined the efficacy and safety of drugs to treat narcolepsy in children and adolescents.

In narcolepsy with cataplexy, pharmacological treatment for daytime sleepiness involves modafinil or amphetamine-like stimulants, which likely act through increasing dopamine transmission. Cataplexy and abnormal REM sleep symptoms, sleep paralysis and hallucinations, are typically treated with tricyclic antidepressants or serotonin and norepinephrine reuptake inhibitors. Adrenergic reuptake inhibition is believed to be the primary mode of action. Sodium oxybate, or gamma hydroxybutyric acid, is also used at night to consolidate disturbed nocturnal sleep. This treatment is also effective on cataplexy and other symptoms.

The treatment of narcolepsy without cataplexy and idiopathic hypersomnia uses similar compounds, most notably modafinil and amphetamine-like stimulants (Billiard and Dauvilliers, 2001). Treatments, with the possible exception of lithium, of periodic hypersomnia and Kleine-Levin syndrome type are typically ineffective (Arnulf et al., 2005a).

PARASOMNIAS

Manifestations and Prevalence

Parasomnias are unpleasant or undesirable behaviors or experiences that occur during entry into sleep, during sleep, or during arousals from sleep (AASM, 2005). They are categorized as primary parasomnias, which predominantly occur during the sleep state, and secondary parasomnias, which are complications associated with disorders of organ systems that occur during sleep. Primary parasomnias can further be classified depending on which sleep state they originate in, REM sleep, NREM, or others that can occur during either state (Table 3-4).

Parasomnias typically manifest themselves during transition periods from one state of sleep to another, during which time the brain activity is reorganizing (Mahowald and Schenck, 2005). Activities associated with parasomnias are characterized by being potentially violent or injurious, disruptive to other household members, resulting in excessive daytime sleepiness, or associated with medical, psychiatric, or neurological conditions (Mahowald and Ettinger, 1990).

Disorders of Arousal, NREM

Disorders of arousal are the most common type of parasomnia, occurring in as much as 4 percent of the adult population (Ohayon et al., 1999) and up to 17 percent of children (Klackenberg, 1982). Typically the arousals occur during the first 60 to 90 minutes of sleep and do not cause full awakenings, but rather partial arousal from deep NREM sleep. Disorders of arousal manifest in a variety of ways, from barely audible mumbling, disoriented sleepwalking, to frantic bouts of shrieking and flailing of limbs (Wills and Garcia, 2002).

Confusional Arousals

Individuals who experience confusional arousals exhibit confused mental and behavioral activity following arousals from sleep. They are often disoriented in time and space, display slow speech, and blunted answers to questions (AASM, 2005). Episodes of resistive and even violent behavior can last several minutes to hours. Confusional arousals are more than three to four times more prevalent in children compared to individuals 15 years or older (around 3 percent) (Ohayon et al., 2000). They can be precipitated by forced arousals, particularly early in an individual's sleep cycle.

TABLE 3-4 Selected Primary Sleep Parasomnias

Name	Description
Disorders of arousal associated with NREM sleep	
Confusional arousals	Individuals display mental confusion or confusional behavior during or following arousal, typically from SWS
Sleepwalking	Involves a series of behaviors initiated during arousals from SWS that culminate in walking around in an altered state of consciousness
Sleep terrors	Typically initiated by a loud scream associated with panic, followed by intense motor activity, which can result in injury
Disorders associated with REM sleep	
Nightmare disorder	Recurrent nightmares that are coherent dream sequences manifest as disturbing mental experiences that generally occur during REM sleep
REM sleep behavior disorder	A complex set of behaviors, including mild to harmful body movements associated with dreams and nightmares and loss of muscle atonia
Recurrent isolated sleep paralysis	Inability to speak or move, as in a temporary paralysis, at sleep onset or upon waking
Other parasomnias	
Enuresis	Involuntary release of urine
Nocturnal groaning (catathrenia)	Characterized by disruptive groaning that occurs during expiration, particularly during the second half of night
Sleep-related eating disorder	Marked by repeated episodes of involuntary eating and drinking during arousals from sleep
Sleep-related dissociative disorders	A dissociative episode that can occur in the period from wakefulness to sleep or from awakening from stages 1 or 2 or from REM sleep
Exploding head syndrome	Characterized by a sudden, loud noise or explosion in the head; this is an imagined, painless noise.
Sleep-related hallucinations	Hallucinatory images that occur at sleep onset or on awakening

NOTE: NREM, non-rapid eye movement; REM, rapid eye movement; SWS, slow-wave sleep.
SOURCES: Halasz et al. (1985), Terzano et al. (1988), Zucconi et al. (1995), Zadra et al. (1998), and AASM (2005).

Sleepwalking

Sleepwalking is characterized by a complex series of behaviors that culminate in walking around with an altered state of consciousness and impaired judgment (AASM, 2005). Individuals who are sleepwalking commonly perform routine and nonroutine behaviors at inappropriate times and have difficulty recalling episodic events. Like confusional arousals, the prevalence of sleepwalking is higher in children than adults (AASM, 2005).

There appears to be a genetic predisposition for sleepwalking. Children who have both parents affected by sleepwalking are 38 percent more likely to also be affected (Klackenberg, 1982; Hublin et al., 1997).

Sleep Terrors

Sleep terrors are characterized by arousal from SWS accompanied by a cry or piercing scream, in addition to autonomic nervous system and behavioral manifestations of intense fear (AASM, 2005). Individuals with sleep terrors are typically hard to arouse from sleep and, when they are awoken, are confused and disoriented. There does not appear to be a significant gender or age difference in prevalence or incidence of sleep terrors (AASM, 2005).

Disorders Associated with REM Sleep

Rapid Eye Movement Sleep Behavior Disorder

REM sleep behavior disorder is characterized by a complex set of behaviors that occur during REM sleep, including mild to harmful body movements associated with dreams and nightmares (AASM, 2005). Normally during REM sleep, muscles are temporarily paralyzed; however, in REM sleep behavior disorder this paralysis is absent, thus allowing individuals to “play out” their dreams. The overall prevalence in the general population is estimated to be less than half a percent, slightly higher in older persons (AASM, 2005), and affecting men more frequently than women.

REM sleep behavior disorder is frequently associated with neurological disorders and it has been suggested that it could be an early sign of neurodegeneration (Olson et al., 2000). At least 15 percent of individuals with Parkinson’s disease (Comella et al., 1998; Gagnon et al., 2002) and 44 percent of individuals with multiple system atrophy (Plazzi et al., 1997; 1998) also suffer from REM sleep behavior disorder. There are a number of effective pharmacological treatments, including a long-acting benzodiazepine (Schenck and Mahowald, 1990), clonazepam (Schenck et al., 1993), and dopamine agonists (Bamford, 1993; Fantini et al., 2003).

Nightmare Disorder

Nightmare disorder is characterized by recurrent disturbances of dreaming that are disturbing mental experiences that seem real and sometimes cause the individual to wake up. If awoken, individuals commonly have difficulty returning to sleep. Nightmares often occur during the second half of a normal period of sleep. Dream content involves a distressing theme, typically imminent physical danger. During nightmares, individuals experience increased heart and respiration rates (Fisher et al., 1970; Nielsen and Zadra, 2000).

Nightmares commonly affect children and adolescents and decrease in frequency and intensity as an individual grows older (AASM, 2005). Drugs and alcohol can trigger nightmares. Prevalence rates are also higher in individuals suffering from acute stress disorder and posttraumatic stress disorder.

SLEEP AND NEUROLOGICAL DISORDERS

Individuals suffering from dementia commonly experience sleep abnormalities. Although there are a variety of conditions associated with dementia—Alzheimer’s disease, Parkinson’s disease, dementia with Lewy bodies, Huntington’s disease, and Creutzfeldt-Jakob disease—there are some common patterns of sleep impairment associated with all dementias. Typically, sleep is more fragmented, leading to more awakenings and consequently less time asleep, and REM may be decreased (Petit et al., 2005). These sleep impairments usually worsen as the disease progresses.

Alzheimer’s Disease

Manifestations and Prevalence

Alzheimer’s disease is a neurodegenerative disorder characterized by memory loss and an intellectual decline that progresses with age and is caused by the degeneration of neurons in the brain. It is estimated that about 4 million individuals in the United States suffer from Alzheimer’s disease. Approximately one-quarter of these individuals have sleep disturbances (Tractenberg et al., 2005; Moran et al., 2005). Alzheimer’s disease causes an increase number of arousals and affects an individual’s sleep architecture. As a result of an increase in duration and number of awakenings, individuals spend an increased percentage of time in stage 1 sleep and a reduced percentage in stage 2 and SWS (Prinz et al., 1982a,b; Reynolds et al., 1985; Montplaisir et al., 1995).

Etiology and Risk Factors

There is limited information regarding the etiology of sleep disorders associated with Alzheimer’s disease and other conditions that cause dementia. Associations with sleep disturbance and other behavioral symptoms have been identified, including aggressiveness (Moran et al., 2005) and depression (Tractenberg et al., 2005). However, the pathophysiology of this association is not known. In addition to behavioral symptoms, OSA may also occur at a higher prevalence in individuals with Alzheimer’s disease than in the general population (Bliwise, 2002).

Treatment

Treatment options for demented individuals who suffer sleep disorders are typically the same as those received by individuals who do not have dementia. The approach is to address the sleep disorder based on its symptoms while managing and treating the underlying medical or psychiatric disorder (Petit et al., 2005). However, treating an individual's sleep disorder is not effective in reducing dementia associated with Alzheimer's disease.

Parkinson's Disease

Manifestations and Prevalence

Sleep complaints and subsequent diminished quality of life are common in individuals who suffer from Parkinson's disease. Parkinson's disease is a neurological disorder that primarily affects the elderly—0.9 percent of people 65 to 69 years of age to upwards of 5 percent of people 80 to 84 years of age have Parkinson's disease (de Rijk et al., 1997). It is characterized by trouble initiating walking and other movements, muscle tremor, a slow gait, and reduced facial expressions. Sleep disturbances associated with Parkinson's disease include difficulty falling asleep, nocturnal akinesia, altered sleep architecture, abnormal motor activity, periodic limb movements, REM sleep behavior disorder (see above), and disturbed breathing. During the day, many Parkinson patients have excessive sleepiness.

Sleep disturbances typically increase with disease progression. Individuals suffer from increased sleep latency and frequent awakenings, spending as much as 30 to 40 percent of the night awake (Kales et al., 1971; Bergonzi et al., 1975). This causes reduced time spent in stages 3 and 4 and REM sleep and increased duration in stages 1 and 2 (Kales et al., 1971).

Etiology and Risk Factors

Sleep patterns are affected by abnormalities caused by neurodegeneration in regions of the brain that are involved in regulating the sleep-wake cycle. Dopaminergic neurons in the substantia nigra are dramatically reduced in number, as are noradrenergic neurons in the locus coeruleus (Jellinger, 1986) and cholinergic neurons in the pedunculopontine nucleus (Zweig et al., 1989). Braak and colleagues (2004) examined a large series of autopsy brains. They found that Lewy body degeneration begins in the lower brainstem and ascends to involve the substantia nigra only after several years, consistent with observations that REM alterations may precede the movement disorder by several years in many Parkinson's disease patients. REM sleep behavioral disorder is often seen in patients with Parkin-

son's disease and other parkinsonian syndromes, such as multiple systems atrophy and progressive supranuclear palsy. The ability to ameliorate the symptoms of REM sleep behavioral disorder with dopaminergic agonist drugs suggests that it may be an early sign of damage to the dopaminergic system (Trampus et al., 1991).

Treatment

Treating sleep disturbances associated with Parkinson's disease is complicated owing to the different actions associated with dopaminergic medications. Medications used to treat this disorder often include dopamine precursors (levodopa/carbidopa) and dopamine agonists (pramipexole and ropinirole). When used in low doses, these medications can promote sleep, but high doses may cause increased nocturnal wakefulness, decreased SWS, and decreased sleep continuity (Leeman et al., 1987; Monti et al., 1988; Cantor and Stern, 2002). In contrast, excessive daytime sleepiness, including sleep attacks, has also been described in association with dopamine agonists (Paus et al., 2003); therefore, many patients with Parkinson's disease require daytime stimulants such as modafinil or amphetamine to relieve excessive sleepiness.

Other classes of medication used to treat Parkinson's disease include monoamine oxidase-B inhibitors (selegiline), presynaptic relating agents (amatiadine, anticholinergic agents), and catechol-O-methyltransferase (COMT) inhibitors (hyoscyaine, benztropine). All may potentially affect sleep (Chrisp et al., 1991), particularly with regard to decreasing REM sleep, but the sleep effects of these medications remain to be well described (Kaakkola, 2000).

Epilepsy

Manifestations and Prevalence

Epilepsy refers to a group of various disorders characterized by abnormal electrical activity in the brain that manifests itself in individuals as a loss of or impaired consciousness and abnormal movements and behaviors. Sleep, sleep deprivation, and seizure activity are tightly intertwined. After stroke and Alzheimer's disease, epilepsy is the third most common neurological disorder in the United States, with incidence between 1.5 to 3.1 percent (Shouse and Mahowald, 2005). It is estimated that sleep-related epilepsy may affect as many as 10 percent or more of epileptic individuals (AASM, 2005). Sixty percent of individuals who suffer partial complex localization related seizures—21.6 percent of the general epileptic population—exhibit convulsions only during sleep (Janz, 1962).

Disorders that cause seizures may affect an individual's sleep cycle, leading to sleep deprivation. Similarly, sleep and sleep deprivation increase the incidence of seizure activity. Sleep-related epilepsy normally presents with at least two of the following features: arousals, abrupt awakenings from sleep, generalized tonic-clonic movements of the limbs, focal limb movement, facial twitching, urinary incontinence, apnea, tongue biting, and postictal confusion and lethargy (AASM, 2005). These features cause sleep fragmentation and daytime fatigue.

There are a number of common epileptic syndromes that manifest solely or predominately during the night, including nocturnal frontal lobe epilepsy, benign epilepsy of childhood with centrotemporal spikes, early-onset or late-onset childhood occipital epilepsy, juvenile myoclonic epilepsy, and continuous spike waves during non-REM sleep. Nocturnal frontal lobe epilepsy is characterized by severe sleep disruption, injuries caused by involuntary movements, and occasional daytime seizures. Juvenile myoclonic epilepsy is characterized by synchronous involuntary muscle contractions that often occur during awakening. Continuous spike waves during non-REM sleep epilepsy are commonly associated with neurocognitive impairment and sometimes with impairment of muscle activity and control.

Etiology and Risk Factors

Risk factors for sleep-related epilepsy include stress, sleep deprivation, other sleep disorders, and irregular sleep-wake rhythms. The etiologies for nocturnal seizures are not clearly understood. Genetic factors are likely important; however, as of yet no pathogenic markers have been associated with sleep-related epilepsy. There are specific patterns of rhythmic activity among neurons within specific regions of the brain—the hypothalamus and brainstem—that regulate sleep and arousal. Association of specific neuronal activity between these different regions is important for regulating sleep, while bursts of disassociated neuronal activity may contribute to nocturnal seizures (Tassinari et al., 1972; Velasco and Velasco, 1982; Applegate et al., 1986; Shouse et al., 1996).

Treatment

Treatments for seizures caused by sleep-related epileptic syndromes are typically similar to those of other seizure disorders (Dreifuss and Porter, 1997). Individuals with epilepsy are susceptible to nocturnal sleep disturbance and daytime sleepiness associated with commonly used medications. However, daytime hypersomnolence is not always treatable with antiepileptic drugs (Palm et al., 1992). In particular, phenobarbital, a mainstay of treatment for many years, causes daytime sedation in a dose depen-

dent manner (Brodie and Dichter, 1997). Daytime sedation is also observed with other antiepileptic agents including carbamazepine, alproate, phenytoin, and primidone. Some of the newer medication such as gabapentin, lamotrigine, bigabatratin, and zonisamide are often better tolerated (Salinsky et al., 1996). In addition to daytime sedation, these drugs also cause increased nocturnal sleep time. Vagal nerve stimulation, however, has been reported to improve daytime alertness (Rizzo et al., 2003), but it may also induce sleep apnea (Holmes et al., 2003).

Stroke

Manifestations and Prevalence

Stroke results in a sudden loss of consciousness, sensation, and voluntary movement caused by disruption of blood flow—and therefore oxygen supply—to the brain. Following a stroke an individual's sleep architecture is often altered, causing a decrease in the total sleep time, REM sleep, and SWS (Broughton and Baron, 1978). Insomnia is a common complication of stroke that may result from medication, inactivity, stress, depression, and brain damage.

The annual incidence of stroke is 2 to 18 per 1000 individuals, and sleep-wake disturbances are found in at least 20 percent of stroke patients (Bassetti, 2005). In addition, over 70 percent of individuals who have suffered a mild stroke and are under 75 years of age suffer fatigue (Carlsson et al., 2003).

Sleep-Disordered Breathing May Be a Risk Factor

Risk factors for stroke include heart disease, hypertension, alcohol abuse, transient ischemic attacks, and, as described above, possibly sleep-disordered breathing (Diaz and Sempere, 2004). Studies investigating the association between sleep-disordered breathing and stroke found that 60 to 70 percent of individuals who have suffered a stroke exhibit sleep-disordered breathing with an apnea-hypopnea index of 10 or greater (Dyken et al., 1996; Bassetti et al., 1996). Sleep-disordered breathing has also been found in a high frequency of individuals with transient ischemic attacks (McArdle et al., 2003), hypertension (Morrell et al., 1999), myocardial infarction, and heart failure (Good et al., 1996; Shamsuzzaman et al., 2003).

Treatment

There are no specific therapies that relieve sleep-related symptoms caused by a stroke. Rather, treatments depend on the specific symptoms and are similar to the treatments of sleep disorders that arise indepen-

dent of a stroke. For example, CPAP is the treatment of choice for sleep disordered breathing, and insomnia and parasomnias are treated using similar temporary hypnotic drug therapies as typically used, zolpidem or benzodiazepines. However, treatments for hypersomnia are not always as effective following a stroke (Bassetti, 2005).

SUDDEN INFANT DEATH SYNDROME

Manifestations and Prevalence

Sudden infant death syndrome (SIDS), the sudden and unexpected death of infants less than a year old during sleep, has no known cause (American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome, 2005; CDC, 2006). The syndrome is currently the third most common cause of infant death in the United States (CDC, 2006), responsible for approximately 3,000 infant deaths a year in this country (NICHD, 2006b). The majority of SIDS-related deaths occur in infants who are between 2 and 4 months old (NICHD, 2006a).

Etiology and Risk Factors

Although there are no known causes for SIDS, various hypotheses exist about the mechanisms underlying the syndrome. The leading theory is that developmental abnormalities in the infant's cardiorespiratory system increase the child's susceptibility to suffocation (Meny et al., 1994; Kinney et al., 1995; Verrier and Josephson, 2005). Infants who later die of SIDS have higher heart rates, narrower heart rate ranges, and problems with coordination of respiration, heart rate, and arterial blood pressure while sleeping (Kemp and Thach, 1991; Schechtman et al., 1995; Kinney et al., 1995; Verrier and Josephson, 2005). This lack of coordination in the cardiorespiratory system may be a result of defects in the region of the brain responsible for controlling breathing and arousal (Kinney et al., 1995; Panigraphy et al., 1997; AAP, 2000), possibly resulting in a baby being unable to wake up in response to troubled breathing.

Concordantly, risk factors attributed to SIDS typically relate to an infant's ability to breathe easily while sleeping. The chief risk factor for SIDS is a prone sleeping position, otherwise known as stomach sleeping (Dwyer et al., 1991; Ponsonby et al., 1993; Irgens et al., 1995). More recently, side sleeping is thought to be attended by an intermediate level of risk (American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome, 2005; CDC, 2006). Other factors related to obstructed breathing space include bed sharing with adults or several family members, soft

sleep surfaces and/or loose bedding and overheating while sleeping (Hauck and Kemp, 1998; AAP, 2000).

Vulnerability to SIDS seems to depend on both gender and ethnicity. Male infants are more likely to die of SIDS than female babies (NICHD, 2006a); African American infants have twice the likelihood as Caucasian infants of dying from SIDS (Hauck et al., 2003; Daley, 2004; NICHD, 2006a), while Native American infants are three times as likely to be victims of this syndrome (AAP, 2000). SIDS has also been reported to occur at increased frequency in family members with OSA (Tishler et al., 1996), suggesting that there may be common genetic risk factors for both conditions.

Finally, general measures of poor health form the final category of risk factors. Smoking, drinking, or drug use by the mother during gestation are linked to an increased chance of SIDS-related deaths in infants, as is infant exposure to smoke (Schoendorf and Kiely, 1992; AAP, 2000; Iyasu et al., 2002). Infants born with low body weight, prematurely, or to mothers under the age of 20 are also at higher risk of SIDS (Malloy and Hoffman, 1995; AAP, 2000).

Prevention

Preventive measures have reduced the incidence of SIDS in the United States by more than 50 percent. A number of national intervention programs currently exist through various organizations. Of these, the most prominent intervention program is NIH's "Back to Sleep" campaign (Chapter 5).

Additional preventive measures include no smoking, drinking, or drug use by the mother while pregnant; removal of loose bedding or other items that could suffocate an infant; and prevention of high temperatures in the baby's sleeping environment (NICHD, 2006a).

SLEEP AND MOVEMENT DISORDERS

Restless Legs Syndrome

Manifestations and Prevalence

RLS is a neurological condition characterized by an irresistible urge to move the legs (it also may affect the arms, trunk, or head and neck). It is also associated with paresthesias—uncomfortable feelings—which individuals describe as creepy-crawly, jittery, itchy, or burning feelings. The symptoms are partially or completely relieved by movement. The urge to move and unpleasant sensations worsen during periods of rest or inactivity, espe-

cially in the evening and at night, causing most individuals difficulty falling asleep (Michaud et al., 2000). The discomfort associated with RLS also causes individuals to wake frequently during the night (Montplaisir et al., 1997). Individuals with RLS often experience periodic limb movements; however, periodic limb movement disorder (see below) is not always associated RLS (Michaud et al., 2000).

The prevalence of RLS has been reported to be at minimum 5 percent (Lavigne and Montplaisir, 1994; Rothdach et al., 2000; NSF, 2005a; Montplaisir et al., 2005; Phillips et al., 2006), which makes it one of the most common movement disorders and sleep disorders. This condition may be found in adolescents and teenagers (Kryger et al., 2002a) and is more common in older adults and females (Rothdach et al., 2000; Allen and Earley, 2001; Nichols et al., 2002), affecting over 20 percent of pregnant women. RLS symptoms associated with pregnancy are caused by transient low levels of ferritin and folate; therefore, they typically disappear within 4 weeks after delivery (Lee et al., 2001).

RLS may also be associated with attention-deficit hyperactivity disorder (ADHD). In a cross-sectional survey of 866 children, ADHD symptoms were almost twice as likely to occur with symptoms of RLS as would be expected by chance alone (Chervin et al., 2002).

Etiology and Risk Factors

The exact cause of RLS is not completely understood. It likely results from altered dopamine and iron metabolism, and there is evidence for a genetic contribution. More than 50 percent of idiopathic cases are associated with a positive family history of RLS (Ekbom, 1945; Walters et al., 1996; Montplaisir et al., 1997; Winkelmann et al., 2002; Allen et al., 2003), and these cases segregate in an autosomal dominant fashion with high penetrance (90 to 100 percent) (Winkelmann et al., 2002). Susceptibility gene loci have been identified on chromosomes 12q (Desautels et al., 2001), 14q (Bonati et al., 2003), and 9p (Chen et al., 2004); however, no genetic markers or abnormalities have been identified.

RLS commonly occurs in individuals with iron deficiency, including end-stage renal disease, iron-deficiency anemia, pregnancy, and gastric surgery. Iron deficiency, for example caused by repeated blood donation, may also be associated with RLS (Silber et al., 2003; Ulfberg and Nystrom, 2004; Kryger et al., 2003). It is hypothesized that low levels of iron impair transmission of dopamine signals, which contributes to RLS. Iron levels are reduced in the substantia nigra (Allen et al., 2001; Connor et al., 2003), which is a region of the brain responsible for controlling voluntary movement through neurons that rely on dopamine to communicate with each other. The iron deficiency is consistent with abnormal regulation of the transferrin

receptor, which is responsible for transporting iron across cell membranes. Iron in turn is necessary for the synthesis of dopamine and the activity of the D₂ dopamine receptor (Turjanski et al., 1999). The association between dopamine, iron deficiency, and RLS is further supported by observations that dopamine antagonists usually make RLS symptoms worse (Winkelmann et al., 2001), while dopaminergic agonists are used to treat RLS (Walters et al., 1988; Wetter et al., 1999; Stiasny et al., 2001).

Idiopathic RLS is not associated with an increased mortality rate; however, in secondary cases of RLS, such as in individuals treated with long-term hemodialysis for end-stage renal disease, RLS is associated with a greater mortality risk (Winkelman et al., 1996). In a survey of 894 dialysis patients that rated symptoms of RLS, severe symptoms were associated with an increased hazard ratio (OR = 1.39; 95% CI, 1.08–1.79) (Unruh et al., 2004).

Treatment

There are both behavioral and pharmacological treatments for RLS; however, there have been no clinical trials reporting the efficacy of non-pharmacological strategies to reduce RLS symptoms. Mild to moderate symptoms can sometimes be treated by lifestyle changes, including maintaining a normal sleeping pattern, taking supplements to manage iron deficiencies, and minimizing consumption of alcohol, caffeine, and tobacco (NINDS, 2005).

RLS is primarily treated using one of four classes of prescription medications: dopaminergic agents, benzodiazepines, opioids, or anticonvulsants (central nervous system depressants). Dopaminergic agents are the primary treatment option for individuals with RLS (Hening et al., 2004). Medications include the dopamine precursor levodopa (L-dopa). Although associated with some adverse effects, administration of L-dopa significantly reduces symptoms of RLS and periodic limb movements that occur throughout the night (Brodeur et al., 1988). However, dopaminergic agents can also have a stimulating effect that may exacerbate insomnia. Benzodiazepines are effective in improving sleep continuity and are therefore frequently prescribed in combination with dopaminergic agents. Opioids may be prescribed in patients with severe symptoms to help to induce relaxation and minimize pain (Walters et al., 1993, 2001). However, opioids may also exacerbate sleep apnea; therefore, they should be used cautiously in patients who snore (Montplaisir et al., 2005). Anticonvulsants are commonly prescribed as an alternative to dopaminergic agents, owing to their ability to minimize leg pain (Montplaisir et al., 2005). It is believed that anticonvulsants, such as carbamazepine and gabapentin, are less potent than dopaminergic agents; however, there have been no comparative studies performed. Furthermore,

there have been a limited number of studies that have examined the safety and efficacy of these treatments in children and adolescents.

Periodic Limb Movement Disorder

Periodic limb movement disorder is characterized by disruptions to sleep caused by periodic episodes of limb movements that occur during sleep, which cannot be explained by any other sleep disorder (AASM, 2005). Individuals with periodic limb movement disorder primarily complain of difficulty with sleep onset and sleep maintenance, insomnia, and/or hypersomnia. The periodic limb movements manifest themselves as rhythmic extensions of the big toe, dorsiflexions of the ankle, and occasional flexions of the knee and hip (Coleman, 1982). These are scored using the periodic limb movements index, which examines over the course of an hour the number of movements that are 0.5 to 5 seconds in duration, separated by an interval between 5 to 90 seconds, and in sequence of four or more an hour. An overnight index score of 5 or greater in children and 15 or greater in adults is considered pathogenic (AASM, 2005).

Periodic limb movements typically occur in the lower extremities and may result in autonomic arousal, cortical arousal, or an awakening. However, typically the individual is unaware of the movements. They are more frequent in the beginning of the night and cluster together. These events are associated with a fast heart rate, followed by a period of slow heart rate (Friedland et al., 1985). Periodic limb movements disorder is associated with above average rates of depression, memory impairment, attention deficits, oppositional behaviors, and fatigue (AASM, 2005). Similar to RLS, dopaminergic medications are helpful in alleviating the disorder's symptoms.

Periodic limb movements are believed to be very common, especially in older persons, occurring in 34 percent of individuals over the age of 60 (AASM, 2005). However, the disorder—periodic limb movements associated with sleep disruption—is not as common. Periodic limb movements are very common in RLS, occurring in 80 to 90 percent of individuals. It is also observed in individuals with narcolepsy, REM sleep behavior disorder (Folstein et al., 1975), OSA (Montplaisir et al., 1996), and hypersomnia (Whitehouse et al., 1982). Children with ADHD have an increased prevalence of periodic limb movements (Picchiatti et al., 1998), and children with periodic limb movement disorders are more likely to have ADHD (Picchiatti et al., 1999; Ozminkowski et al., 2004). Sleep-disordered breathing may be a modulator that increases the association between periodic limb movements and ADHD (Chervin and Archbold, 2001).

SLEEP AND MEDICAL DISORDERS

A number of different medical disorders and diseases, from a common cold to cancer, frequently alter an individual's sleep-wake cycle. These sleep problems often result from pain or infection associated with the primary condition. Although these are both known to cause problems with sleep-wake cycles, as will be shown below, very little is still known about the etiology.

Pain

Pain is described as an acute or chronic unpleasant sensory and emotional experience that varies from dull discomfort to unbearable agony that is associated with actual or potential tissue damage. It commonly causes sleep fragmentation and changes in an individual's sleep architecture. The symptoms depend on the type and severity of the pain. They include daytime fatigue and sleepiness, poor sleep quality, delay in sleep onset, and decreased cognitive and motor performance (Table 3-5) (Bonnet and Arand, 2003).

Chronic pain affects at least 10 percent of the general adult population (Harstall, 2003), of whom 50 percent complain of poor sleep (Atkinson et al., 1988; Dao et al., 1994; Morin et al., 1998; Roizenblatt et al., 2001; Riley et al., 2001; Dauvilliers and Touchon, 2001; McCracken and Iverson, 2002; Perlis et al., 2005), and 44 percent complain of insomnia (Moldofsky, 2001). There are a number of clinical pain conditions that individuals report affect their sleep quality—RLS, irritable bowel, gastric ulcer, cancer, musculoskeletal disorders, dental and orofacial pain, spinal cord damage, burns, and other trauma (Lavigne et al., 2005).

Although progress has been made, there are still many unanswered questions about how pain affects regions of the brain responsible for regulating the sleep-wake cycle. Neurons that carry pain information to the brain do communicate with regions of the brain that are responsible for arousal—raphe magnus “off” cells (Foo and Mason, 2003). However, it is not known if *hypocretin* and other genes that regulate the circadian rhythms are affected by acute or chronic pain. Further, it is not known whether the hypothalamus, which is involved in sleep homeostasis, is affected by chronic pain (Kshatri et al., 1998; Mignot et al., 2002b). Because little is known about the interaction between pain and the circuitry in the brain that is responsible for regulating the sleep-wake cycle, much of the management of sleep problems focuses on managing and alleviating the pain or sleep quality.

TABLE 3-5 Selected Sleep-Related Symptoms and Findings in the Presence of Pain

Bedtime symptoms

- Delay in sleep onset
- Anxiety, rumination
- Intense fatigue and more intense pain

Sleep time findings

- Lower sleep efficacy (less than 90%)
- Longer percentage sleep time in stage 1, with less in stages 3 and 4
- Numerous sleep stage shifts (stages 3 and 4 toward stages 2 or 1)
- Fragmentation of sleep continuity (increase in number of microarousals, awakenings, sleep stage shifts, respiratory events, movement intrusions)
- Alpha electroencephalographic intrusions in stages 3 and 4 with or without elevated phasic arousals (cyclic alternating pattern)
- Absence of reduction in heart rate variability in sleep (cardiac sympathetic overactivation)
- Nightmares, periodic leg movements, apnea, sweating, heart palpitations
- Wake time in sleep with pain (e.g., neck, lower back, visceral, tooth)

Wake time symptoms

- Unrefreshing sleep sensation, fatigue, headache, etc.
 - Sleepiness if driving
 - Anxiety and anger over fulfilling daytime requirements at home or work
-

SOURCE: Lavigne et al. (2005).

Infectious Disease

Infections caused by bacterial strains, viruses, and parasites may result in changes to sleep patterns. Although it is accepted that the activity of the immune system affects an individual's sleep-wake cycle, very little is known about how these two systems interact. This is complicated by the unique effects that specific infections have on sleep patterns and the absence of a large body of clinical research.

Bacterial Infections and Sleep

Bacterial infections typically cause an increase in the total time spent in SWS and a decreased duration of REM sleep (Toth, 1999; Toth and Opp, 2002). Alterations of sleep patterns can be affected by the type of bacterial infection (Opp and Toth, 2003). For example, gram-negative bacteria induce enhanced sleep more rapidly than do gram-positive bacteria. Differences in the process and progression of the disease also affect the sleep-wake cycle.

Viral Infections and Sleep

Viral infections also have effects on the sleep-wake cycle. Individuals inoculated with rhinovirus or influenza virus report less sleep during the incubation period, while during the symptomatic period they slept longer (Smith, 1992). However, compared to healthy individuals there were no reported difference in sleep quality and number of awakenings.

The human immunodeficiency virus (HIV) also has been shown to alter sleep patterns. Individuals spend increased time in SWS during the second half of night (Darko et al., 1995) and suffer from frequent arousals and decreased time in REM sleep (Norman et al., 1990). As the infection progresses to AIDS, individuals develop increased sleep fragmentation, significant reductions in SWS, and disruption to the entire sleep architecture (Norman et al., 1990; Darko et al., 1995).

Cancer

Many patients with cancer also suffer pain or depression, which contributes to difficulty sleeping. These require treatment as in other patients with pain or depression as causes of insomnia. Excessive sleepiness may be caused by injury to the ascending arousal system due to brain metastases or by leptomeningeal carcinomatosis. These signs often alert physicians to the need to treat the underlying spread of cancer to the central nervous system. Other patients with cancer may develop antitumor antibodies that attack the brain. In particular, anti-Ma-2 antibodies tend to cause hypothalamic lesions and may precipitate daytime sleepiness and even cataplexy (Rosenfeld et al., 2001). Treatment of the underlying cancer may reverse the symptoms in some cases.

Sleeping Sickness

Fungal and parasitic infections also can alter the sleep-wake cycle. For example, sleeping sickness, or African trypanosomiasis, commonly occurs in individuals who have been infected with the *Trypanosoma brucei* (*Tb*) parasite. It is characterized by episodes of nocturnal insomnia and daytime sleep, but not hypersomnia (Lundkvist et al., 2004).

Sleeping sickness is found primarily in sub-Saharan African countries, where *Tb* is transmitted to humans as a result of bites received from tsetse flies (Lundkvist et al., 2004). The prevalence of this disorder is not known; however, over 60 million people live in areas where the *Tb* parasite is endemic.

Sleeping sickness is associated with altered sleep architecture. EEG recordings of individuals with sleeping sickness from Gambia demonstrate

periods of REM sleep that occur throughout the entire sleep-wake cycle, frequently without normal intermediate NREM periods (Buguet et al., 2001). Circadian fluctuations of hormones—cortisol, prolactin, and growth hormone—are also altered in individuals with sleeping sickness (Radomski et al., 1994). Therefore, it has been hypothesized that sleeping sickness may be a circadian rhythm disease that affects the neural pathways that interconnect the circadian-timing and sleep-regulating centers (Lundkvist et al., 2004).

Treatment Effects on Sleep

Numerous medical conditions are associated with a wide variety of sleep disorders including insomnia, hypersomnia, parasomnias, and sleep-related movement disorders. Although these disease-related sleep disorders have recently been receiving an increasing amount of attention, including addition to the latest International Classification of Sleep Disorders (AASM, 2005), the contribution that treatments for these medical conditions make to the development of sleep disturbances is less well appreciated. However, many medical therapies have iatrogenic effects on sleep-wake regulatory systems causing disturbed sleep, daytime sleepiness, and other related side effects.

Treatments for Cardiovascular Disease

Cardiovascular diseases, sometimes associated with sleep-related breathing disorders (Peters, 2005) (see above), are commonly treated with a wide range of medications including antihypertensives, hypolipidemics, and antiarrhythmics; each class of medication can adversely affect sleep and/or waking. For example, beta-antagonists, the mainstay of treatment for hypertension, are commonly associated with fatigue, insomnia, nightmares, and vivid dreams (McAinsh and Cruickshank, 1990). Sleep disturbances appear to be more severe with lipophilic drugs (e.g., propranolol) than with hydrophilic drugs (e.g., atenolol). However, even atenolol, one of the most hydrophilic beta-blockers, has been shown to increase total wake time (Van Den Heuvel et al., 1997). The mechanism underlying sleep disruption by beta-blocking agents may be their tendency to deplete melatonin, an important sleep-related hormone (Garrick et al., 1983; Dawson and Encel, 1993). Fatigue and somnolence have also been reported with other antihypertensive medications such as carvedilol, labetalol, clonidine, methyldopa, and reserpine (Paykel et al., 1982; Miyazaki et al., 2004). In contrast, angiotensin-converting enzyme inhibitors generally have very few effects on sleep (Reid, 1996). Hypolipidemic drugs, including atorvastatin and lovastatin, have

also been associated with reports of insomnia, but placebo-controlled clinical trials of lovastatin, simvastatin, and pravastatin did not appear to increase sleep disturbance (Bradford et al., 1991; Keech et al., 1996). Amiodarone, a widely used antiarrhythmic agent (Hilleman et al., 1998), can cause nocturnal sleep disturbance, and digoxin has been associated with both insomnia and daytime fatigue (Weisberg et al., 2002).

Treatments for Cancer

Patients with cancer receive multiple types of treatments designed at controlling the disease process including chemotherapy, biotherapy, radiotherapy, and medications. All can have important adverse effects on regulating the sleep-wake cycle. For example, sleep problems have been reported in patients undergoing chemotherapy (Broeckel et al., 1998; Berger and Higginbotham, 2000; Lee et al., 2004). However, objective measures of sleep in the patients and analyses of clinical correlates are very limited. Thus, the mechanisms underlying these sleep problems are poorly understood. Menopausal symptoms arising from chemotherapy and hormonal therapy, especially those of a vasomotor type (e.g., hot flashes, sweating), may be a contributing factor (Rombaux et al., 2000; Mourits et al., 2001; Carpenter et al., 2002). Nocturnal sleep disturbances and daytime sleepiness have also been reported in patients undergoing radiotherapy (Beszterczey and Lipowski, 1977; Miaskowski and Lee, 1999).

Cytokines (biotherapy), a diverse group of peptide molecules that regulate cell functions, are sometimes used as adjunct therapy (Dunlop and Campbell, 2000). Interferon, interleukin-2, and tumor necrosis factor are associated with a variety of side effects including daytime sleepiness, disturbed sleep, and depression (Capuron et al., 2000). Although very effective in reducing cancer-related pain, opioids often cause sleep disturbance and are associated with decreased REM and SWS (Cronin et al., 2001).

Treatments for Renal Disease

RLS, periodic limb movement disorder, sleep apnea, and excessive daytime sleepiness affect up to 70 percent of patients with end-stage renal disease receiving treatment with hemodialysis (Parker et al., 2000; Parker, 2003). Hemodialysis may alter biological systems controlling processes that regulate the sleep-wake cycle via several potential mechanisms. The rapid fluid, electrolyte, and acid/base changes that occur are often associated with central nervous system symptoms such as headache, restlessness, changes in arousal, and fatigue during or immediately after treatment. Several studies have reported an increase in cytokine production secondary to blood interactions with bioincompatible aspects of hemodialysis (such as blood expo-

sure to membranes, tubing, and cellular mechanical trauma) and backflow of endotoxins through the membrane (Panichi et al., 2000). Interleukin-1, tumor necrosis factor- α , and interleukin-6 are the major proinflammatory cytokines that may be involved (Pertosa et al., 2000). These substances have both somnogenic and pyrogenic properties and have been linked to a number of postdialytic symptoms (Konsman et al., 2002), including daytime sleepiness and sleep disturbances (Raison and Miller, 2001; Capuron et al., 2002). Dialysis-associated changes in melatonin levels and pattern of secretion and alterations in body temperature rhythm may also play a role in disrupting circadian systems (Vaziri et al., 1993, 1996; Parker et al., 2000; Parker, 2003).

Treatments for Rheumatologic and Immunologic Disorders

Numerous other classes of medications can alter sleep and waking. Corticosteroids are a class of medications that are used to treat a variety of medical conditions including rheumatologic and immunologic disorders, cancer, and asthma. Sleep disturbances, insomnia, daytime hyperactivity, and mild hypomania are common side effects (Wolkowitz et al., 1990); a significant decrease in REM sleep may also occur (Born et al., 1987). Theophylline, a respiratory stimulant and bronchodilator, is in the same class of medications as caffeine and can likewise disturb sleep—even in healthy subjects (Kaplan et al., 1993). Nonsteroidal anti-inflammatory agents may also affect sleep as they decrease the production of sleep-promoting prostaglandins, suppress normal surge of melatonin, and alter the daily rhythm of body temperature (Murphy et al., 1994, 1996). Pseudoephedrine and phenylpropanolamine, which have many of the same pharmacological properties of ephedrine, also cause sleep disruption—and many of these preparation are readily available over the counter (Lake et al., 1990; Bertrand et al., 1996).

Although the medications and treatments listed above are often necessary, it is essential for patients to be aware of potential side effects relating to the sleep-wake-related cycle. Unfortunately, patients often neglect to report such complaints as they think nothing can be done to alleviate the problems. However, numerous behavioral and pharmacological interventions are available to treat these iatrogenically induced problems with the sleep-wake cycle. In addition, administering treatment or medications at appropriate times of day in relationship to the sleep-wake schedule may potentially be beneficial and enhance clinical outcomes (Levi, 1994; Bliwise et al., 2001; Hermida and Smolensky, 2004). Research in this area is greatly needed.

BOX 3-3 **Shift Work Disorder and Jet Lag**

Shift Work Disorder

Shift work type circadian rhythm sleep disorder is characterized by complaints of insomnia or excessive sleepiness resulting from work hours that occur during the normal sleep period, including, night shifts, early morning shifts, and rotating shifts. Total sleep time is normally reduced by 1 to 4 hours and sleep quality is disturbed. During work shifts individuals can experience excessive sleepiness, reduced alertness, and reduced performance capacity. Individuals are also commonly more irritable, and the disorder may have negative social consequences. The condition is closely linked to work schedules; consequently, it abates in response to a conventional sleep schedule.

Jet Lag

Jet lag type is a temporary circadian rhythm sleep disorder that occurs when there is a transitory mismatch between the timing of the sleep-wake cycle caused by a change in time zone. Individuals with jet lag potentially experience disturbed sleep, decreased subjective alertness, general malaise, somatic symptoms such as gastrointestinal disturbance, and impaired daytime function. The severity and the duration of the symptoms are usually dependent on the number of time zones traveled and the direction of travel—eastern travel and travel through multiple time zones typically result in worse symptoms than western travel.

CIRCADIAN RHYTHM SLEEP DISORDERS

Circadian rhythm sleep disorders arise from chronic alterations, disruptions, or misalignment of the circadian clock in relation to environmental cues and the terrestrial light-dark cycle. The 2005 update of the International Classification of Sleep Disorders designated nine different circadian disorders, including delayed sleep phase type, advanced sleep phase type, nonentrained sleep-wake type, irregular sleep-wake type, shift work type, and jet lag type (Box 3-3) (AASM, 2005). These disorders may be comorbid with other neurological or psychiatric disorders, making the diagnosis and treatment difficult (Reid and Zee, 2005). Diagnosis with a circadian rhythm disorder requires meeting the following three criteria:

- Persistent or recurrent pattern of sleep disturbance due primarily to either an alteration of the circadian timekeeping system or a misalignment

between endogenous circadian rhythm and exogenous factors that affect timing and duration of sleep.

- Circadian-related disruption leads to insomnia, excessive sleepiness, or both.
- The sleep disturbance is associated with impairment of social, occupational, or other functions (AASM, 2005).

The following sections will describe two of the nine more common types of circadian rhythm sleep disorders, delayed sleep phase type and advanced sleep phase type.

Delayed Sleep Phase Syndrome

Manifestations and Prevalence

The sleep pattern of individuals suffering from delayed sleep phase syndrome (or delayed sleep phase type) is characterized by sleep onset and wake times that are typically delayed 3 to 6 hours relative to conventional sleep-wake times (Figure 3-7). An individual's total sleep time is normal for his or her age (Weitzman et al., 1981), but individuals typically find it difficult to initiate sleep before 2:00 and 6:00 a.m., and prefer to wake up between 10:00 a.m. and 1:00 p.m. The impact of delayed sleep phase syndrome has not been fully investigated and is therefore limited. In a study that included 14 individuals it was reported that the syndrome may impair an individual's job performance and may be associated with marital problems and financial difficulty (Alvarez et al., 1992). A second study investigated the impact of delayed sleep phase syndrome in 22 adolescents and found an association with increased daytime irritability, poor school performance, and mental disturbances (Regestein and Monk, 1995; AASM, 2005).

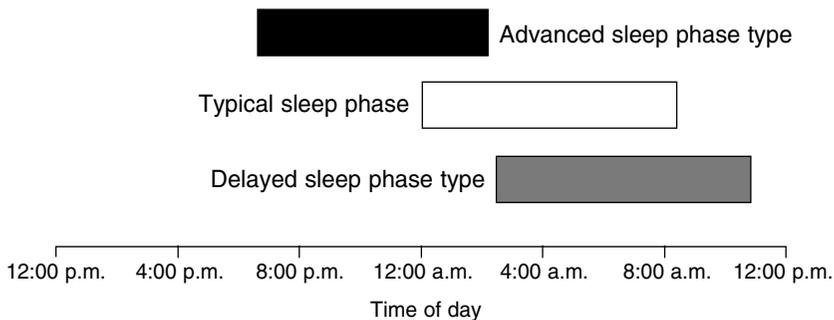


FIGURE 3-7 Representation of the temporal distribution of sleep.
SOURCE: Reid and Zee (2005).

The exact prevalence of delayed sleep phase syndrome in the general population is unknown. It is unclear what the prevalence of this disorder is; however, it may be more prevalent in adolescents and young adults (Weitzman et al., 1981; Pelayo et al., 1988; Regestein and Monk, 1995; AASM, 2005).

Etiology and Risk Factors

Night shift workers may be at higher risk for delayed sleep phase syndrome due to irregular circadian entrainment (Santhi et al., 2005). Similarly, individuals who live in extreme latitudes and are exposed to extended periods of light may also be at increased risk of suffering from delayed sleep phase syndrome (Lingjaerde et al., 1985; Pereira et al., 2005).

Biological, physiological, and genetic factors have been proposed to be responsible for causing delayed sleep phase syndrome. Behaviorally, late bedtimes and rise times delay an individual's exposure to light, which may prevent entraining of the circadian clock. Furthermore, exposure to dim light in the late evening and at night, may also affect the circadian phase (Zeitler et al., 2000; Gronfier et al., 2004).

Biological alterations to the endogenous circadian system also contribute to delayed sleep phase syndrome. Although levels of melatonin typically increase in the evening hours, individuals with this syndrome have a hypersensitivity to nighttime bright light exposure in the suppression of melatonin (Czeisler et al., 1981). It has also been hypothesized that the disorder may result from a circadian phase that has a reduced sensitivity to photic entrainment, or the free-running period of the circadian cycle is prolonged (Czeisler et al., 1981). Consistent with these hypotheses, polymorphisms in circadian genes influence the entraining and free-running period of the circadian cycle and may be associated with delayed sleep phase syndrome (Takahashi et al., 2000; Iwase et al., 2002; Hohjoh et al., 2003; Archer et al., 2003; Pereira et al., 2005). A recent study has also identified a candidate gene, human *PER2*, that results in familial advanced sleep phase syndrome (Xu et al., 2005).

Treatment

Treatment for delayed sleep phase syndrome requires resynchronizing to a more appropriate phase to the 24-hour light-dark cycle. In addition to a structured sleep-wake schedule and good sleep hygiene practices, potential therapies include resetting the circadian pacemaker with bright light, melatonin, or a combination of both. However, studies that have investigated the efficacy of bright light have provided mixed results (Pelayo et al., 1988; Rosenthal et al., 1990; Akata et al., 1993; Weyerbrock et al., 1996), partially owing to limitations in their study design and the numbers of par-

ticipants included in each study. Consequently, there are no standard criteria for its use. Similarly, there have been no large-scale controlled studies examining the efficacy of melatonin, and as of yet it has not been approved by the Food and Drug Administration for this indication (Reid and Zee, 2005).

Advanced Sleep Phase Syndrome

Manifestations and Prevalence

Advanced sleep phase syndrome (or advanced sleep phase type) is characterized by involuntary bedtimes and awake times that are more than 3 hours earlier than societal means (Figure 3-7) (Reid and Zee, 2005). As is the case with delayed sleep phase syndrome, the amount of sleep is not affected, unless evening activities result in later bedtimes. Therefore, the syndrome is primarily associated with impaired social and occupational activities.

The prevalence of advanced sleep phase syndrome is unknown; however, it has been estimated that as many as 1 percent of the middle-aged adults may suffer from it (Ando et al., 1995). One of the challenges in determining its prevalence is that affected individuals typically do not perceive it as a disorder and therefore do not seek medical treatment (Reid and Zee, 2005).

Etiology and Risk Factors

The causes of this syndrome are not known; however, as with delayed sleep phase type, biological and environmental factors likely contribute to the onset of advanced sleep phase type. Several familial cases of this syndrome have been reported (Jones et al., 1999; Ondze et al., 2001; Reid et al., 2001; Satoh et al., 2003), and these cases segregate in a dominant mode. Polymorphisms in circadian clock genes have been identified in a family with advanced sleep phase syndrome (Toh et al., 2001; Shiino et al., 2003). Changes in the activity of genes involved in circadian biology are consistent with observations that individuals with this syndrome have circadian rhythms that are less than 24 hours.

Treatment

Treatment options for individuals with advanced sleep phase syndrome are limited. Bright light therapy in the evening has been used successfully in a limited study to reduce awakenings (Campbell et al., 1993; Palmer et al., 2003). It is also hypothesized that administration of low levels of melatonin

in the early morning may also be used (Lewy et al., 1996), though there are no published reports verifying this option.

REFERENCES

- AAP (American Academy of Pediatrics). 2000. Changing concepts of sudden infant death syndrome: Implications for infant sleeping environment and sleep position. American Academy of Pediatrics. Task Force on Infant Sleep Position and Sudden Infant Death Syndrome. *Pediatrics* 105(3 Pt 1):650–656.
- AASM (American Academy of Sleep Medicine). 2005. *The International Classification of Sleep Disorders*. Westchester, IL: American Academy of Sleep Medicine.
- Akata T, Sekiguchi S, Takahashi M, Miyamoto M, Higuchi T, Machiyama Y. 1993. Successful combined treatment with vitamin B₁₂ and bright artificial light of one case with delayed sleep phase syndrome. *Japanese Journal of Psychiatry and Neurology* 47(2):439–440.
- Al-Delaimy WK, Manson JE, Willett WC, Stampfer MJ, Hu FB. 2002. Snoring as a risk factor for type II diabetes mellitus: A prospective study. *American Journal of Epidemiology* 155(5):387–393.
- Aldrich MS. 1996. The clinical spectrum of narcolepsy and idiopathic hypersomnia. *Neurology* 46(2):393–401.
- Ali NJ, Pitson DJ, Stradling JR. 1993. Snoring, sleep disturbance, and behaviour in 4–5 year olds. *Archives of Disease in Childhood* 68(3):360–366.
- Allen RP, Earley CJ. 2001. Restless legs syndrome: A review of clinical and pathophysiologic features. *Journal of Clinical Neurophysiology* 18(2):128–147.
- Allen RP, Barker PB, Wehr F, Song HK, Earley CJ. 2001. MRI measurement of brain iron in patients with restless legs syndrome. *Neurology* 56(2):263–265.
- Allen RP, Picchietti D, Hening WA, Trenkwalder C. 2003. Restless legs syndrome: Diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Medicine* 4(2):101–119.
- Alvarez B, Dahlitz MJ, Vignau J, Parkes JD. 1992. The delayed sleep phase syndrome: Clinical and investigative findings in 14 subjects. *Journal of Neurology, Neurosurgery, and Psychiatry* 55(8):665–670.
- American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome. 2005. The changing concept of sudden infant death syndrome: Diagnostic coding shifts, controversies regarding the sleeping environment, and new variables to consider in reducing risk. *Pediatrics* 116(5):1245–1255.
- Amin RS, Carroll JL, Jeffries JL, Grone C, Bean JA, Chini B, Bokulic R, Daniels SR. 2004. Twenty-four-hour ambulatory blood pressure in children with sleep-disordered breathing. *American Journal of Respiratory and Critical Care Medicine* 169(8):950–956.
- Amin RS, Kimball TR, Kalra M, Jeffries JL, Carroll JL, Bean JA, Witt SA, Glascock BJ, Daniels SR. 2005. Left ventricular function in children with sleep-disordered breathing. *American Journal of Cardiology* 95(6):801–804.
- Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. 1991. Sleep-disordered breathing in community-dwelling elderly. *Sleep* 14(6):486–495.
- Ancoli-Israel S, Kripke DF, Klauber MR, Parker L, Stepnowsky C, Kullen A, Fell R. 1993. Natural history of sleep-disordered breathing in community dwelling elderly. *Sleep* 16(8 suppl):S25–S29.

- Ancoli-Israel S, Klauber MR, Stepnowsky C, Estline E, Chinn A, Fell R. 1995. Sleep-disordered breathing in African-American elderly. *American Journal of Respiratory Critical Care Medicine* 152(6 Pt 1):1946–1949.
- Ancoli-Israel S, Kripke DF, Klauber MR, Fell R, Stepnowsky C, Estline E, Khazeni N, Chinn A. 1996. Morbidity, mortality and sleep-disordered breathing in community dwelling elderly. *Sleep* 19(4):277–282.
- Ando K, Kripke DF, Ancoli-Israel S. 1995. Estimated prevalence of delayed and advanced sleep phase syndromes. *Sleep Research* 24:509.
- Andreas S, Schulz R, Werner GS, Kreuzer H. 1996. Prevalence of obstructive sleep apnoea in patients with coronary artery disease. *Coronary Artery Disease* 7(7):541–545.
- Anic-Labat S, Guilleminault C, Kraemer HC, Meehan J, Arrigoni J, Mignot E. 1999. Validation of a cataplexy questionnaire in 983 sleep-disorders patients. *Sleep* 22(1):77–87.
- APA (American Psychiatric Association). 1994. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. 4th ed. Washington, DC: American Psychiatric Association.
- Applegate CD, Burchfiel JL, Konkol RJ. 1986. Kindling antagonism: Effects of norepinephrine depletion on kindled seizure suppression after concurrent, alternate stimulation in rats. *Experiments in Neurology* 94(2):379–390.
- Arand D, Bonnet M, Hurwitz T, Mitler M, Rosa R, Sangal RB. 2005. The clinical use of the MSLT and MWT. *Sleep* 28(1):123–144.
- Archer SN, Robilliard DL, Skene DJ, Smits M, Williams A, Arendt J, von Schantz M. 2003. A length polymorphism in the circadian clock gene *Per3* is linked to delayed sleep phase syndrome and extreme diurnal preference. *Sleep* 26(4):413–415.
- Arnulf I, Mabrouk T, Mohamed K, Konofal E, Derenne JP, Couratier P. 2005a. Stages 1-2 non-rapid eye movement sleep behavior disorder associated with dementia: A new parasomnia? *Movement Disorders* 20(9):1223–1228.
- Arnulf I, Zeitzer JM, File J, Farber N, Mignot E. 2005b. Kleine-Levin syndrome: A systematic review of 186 cases in the literature. *Brain* 128(Pt 12):2763–2776.
- Atkinson JH, Slater MA, Grant I, Patterson TL, Garfin SR. 1988. Depressed mood in chronic low back pain: Relationship with stressful life events. *Pain* 35(1): 47–55.
- Ayas NT, White DP, Manson JE, Stampfer MJ, Speizer FE, Malhotra A, Hu FB. 2003. A prospective study of sleep duration and coronary heart disease in women. *Archives of Internal Medicine* 163(2):205–209.
- Babu AR, Herdegen J, Fogelfeld L, Shott S, Mazzone T. 2005. Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea. *Archives of Internal Medicine* 165(4):447–452.
- Baldwin DC Jr, Daugherty SR. 2004. Sleep deprivation and fatigue in residency training: Results of a national survey of first- and second-year residents. *Sleep* 27(2):217–223.
- Bamford CR. 1993. Carbamazepine in REM sleep behavior disorder. *Sleep* 16(1):33–34.
- Bassetti CL. 2005. Sleep and stroke. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 811–830.
- Bassetti C, Aldrich MS. 1999. Sleep apnea in acute cerebrovascular diseases: Final report on 128 patients. *Sleep* 22(2):217–223.
- Bassetti C, Aldrich MS, Chervin RD, Quint D. 1996. Sleep apnea in patients with transient ischemic attack and stroke: A prospective study of 59 patients. *Neurology* 47(5):1167–1173.
- Behlfelt K. 1990. Enlarged tonsils and the effect of tonsillectomy. Characteristics of the dentition and facial skeleton. Posture of the head, hyoid bone and tongue. Mode of breathing. *Swedish Dental Journal: Supplement* 72:1–35.
- Benca RM. 2005a. Diagnosis and treatment of chronic insomnia: A review. *Psychiatry Services* 56(3):332–343.

- Benca RM. 2005b. Mood disorder. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 1311–1326.
- Berger AM, Higginbotham P. 2000. Correlates of fatigue during and following adjuvant breast cancer chemotherapy: A pilot study. *Oncology Nursing Forum* 27(9):1443–1448.
- Bergonzi P, Chiurulla C, Gambi D, Mennuni G, Pinto F. 1975. L-dopa plus dopa-decarboxylase inhibitor. Sleep organization in Parkinson's syndrome before and after treatment. *Acta Neurologica Belgica* 75(1):5–10.
- Bertrand B, Jamart J, Marchal JL, Arendt C. 1996. Cetirizine and pseudoephedrine retard alone and in combination in the treatment of perennial allergic rhinitis: A double-blind multicentre study. *Rhinology* 34(2):91–96.
- Beszterczey A, Lipowski ZJ. 1977. Insomnia in cancer patients. *Canadian Medical Association Journal* 116(4):355.
- Billiard M, Cadilhac J. 1988. Recurrent hypersomnia [in French]. *Revue Neurologique* 144(4):249–258.
- Billiard M, Dauvilliers Y. 2001. Idiopathic hypersomnia. *Sleep Medicine Reviews* 5(5):349–358.
- Billiard M, Dolenc L, Aldaz C, Ondze B, Besset A. 1994. Hypersomnia associated with mood disorders: A new perspective. *Journal of Psychosomatic Research* 38(suppl 1):41–47.
- Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. 1998. Effects of age on sleep apnea in men: I. Prevalence and severity. *American Journal of Respiratory and Critical Care Medicine* 157(1):144–148.
- Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Leiby BE, Vela-Bueno A, Kales A. 2000. Association of hypertension and sleep-disordered breathing. *Archives of Internal Medicine* 160(15):2289–2295.
- Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, Kales A. 2001. Prevalence of sleep-disordered breathing in women: Effects of gender. *American Journal of Respiratory and Critical Care Medicine* 163(3 Pt 1):608–613.
- Bliwise DL. 2002. Sleep apnea, APOE4 and Alzheimer's disease: 20 years and counting? *Journal of Psychosomatic Research* 53(1):539–546.
- Bliwise DL, Bliwise NG, Partinen M, Pursley AM, Dement WC. 1988. Sleep apnea and mortality in an aged cohort. *American Journal of Public Health* 78(5):544–547.
- Bliwise DL, Kutner NG, Zhang R, Parker KP. 2001. Survival by time of day of hemodialysis in an elderly cohort. *Journal of the American Medical Association* 286(21):2690–2694.
- Bonati MT, Ferini-Strambi L, Aridon P, Oldani A, Zucconi M, Casari G. 2003. Autosomal dominant restless legs syndrome maps on chromosome 14q. *Brain* 126(6):1485–1492.
- Bonnet MH, Arand DL. 2003. Clinical effects of sleep fragmentation versus sleep deprivation. *Sleep Medicine Reviews* 7(4):297–310.
- Born J, Zwick A, Roth G, Fehm-Wolfsdorf G, Fehm HL. 1987. Differential effects of hydrocortisone, flucortolone, and aldosterone on nocturnal sleep in humans. *Acta Endocrinologica (Copenhagen)* 116(1):129–137.
- Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. 2004. Stages in the development of Parkinson's disease-related pathology. *Cell and Tissue Research* 318(1):121–134.
- Bradford RH, Shear CL, Chremos AN, Dujovne C, Downton M, Franklin FA, Gould AL, Hesney M, Higgins J, Hurley DP, et al. 1991. Expanded clinical evaluation of lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. *Archives of Internal Medicine* 151(1):43–49.
- Bradley TD, Logan AG, Kimoff RJ, Series F, Morrison D, Ferguson K, Belenkie I, Pfeifer M, Fleetham J, Hanly P, Smilovitch M, Tomlinson G, Floras JS. 2005. Continuous positive airway pressure for central sleep apnea and heart failure. *New England Journal of Medicine* 353(19):2025–2033.

- Breslau N, Roth T, Rosenthal L, Andreski P. 1996. Sleep disturbance and psychiatric disorders: A longitudinal epidemiological study of young adults. *Biological Psychiatry* 39(6): 411–418.
- Brodeur C, Montplaisir J, Godbout R, Marinier R. 1988. Treatment of restless legs syndrome and periodic movements during sleep with L-dopa: A double-blind, controlled study. *Neurology* 38(12):1845–1848.
- Brodie MJ, Dichter MA. 1997. Established antiepileptic drugs. *Seizure* 6(3):159–174.
- Broeckel JA, Jacobsen PB, Horton J, Balducci L, Lyman GH. 1998. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. *Journal of Clinical Oncology* 16(5):1689–1696.
- Brooks B, Cistulli PA, Borkman M, Ross G, McGhee S, Grunstein RR, Sullivan CE, Yue DK. 1994. Obstructive sleep apnea in obese noninsulin-dependent diabetic patients: Effect of continuous positive airway pressure treatment on insulin responsiveness. *Journal of Clinical Endocrinology and Metabolism* 79(6):1681–1685.
- Broughton R, Baron R. 1978. Sleep patterns in the intensive care unit and on the ward after acute myocardial infarction. *Electroencephalography and Clinical Neurophysiology* 45(3):348–360.
- Broughton RJ, Fleming JA, George CF, Hill JD, Kryger MH, Moldofsky H, Montplaisir JY, Morehouse RL, Moscovitch A, Murphy WF. 1997. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. *Neurology* 49(2):444–451.
- Buguet A, Bourdon L, Bouteille B, Cespeglio R, Vincendeau P, Radomski MW, Dumas M. 2001. The duality of sleeping sickness: Focusing on sleep. *Sleep Medicine Reviews* 5(2):139–153.
- Buxbaum SG, Elston RC, Tishler PV, Redline S. 2002. Genetics of the apnea hypopnea index in Caucasians and African Americans: I. Segregation analysis. *Genetic Epidemiology* 22(3):243–253.
- Campbell SS, Dawson D, Anderson MW. 1993. Alleviation of sleep maintenance insomnia with timed exposure to bright light. *Journal of American Geriatric Society* 41(8):829–836.
- Cantor CR, Stern MB. 2002. Dopamine agonists and sleep in Parkinson's disease. *Neurology* 58(4 Suppl 1):S71–S78.
- Caples SM, Gami AS, Somers VK. 2005. Obstructive sleep apnea. *Annals of Internal Medicine* 142(3):187–197.
- Capuron L, Ravaud A, Dantzer R. 2000. Early depressive symptoms in cancer patients receiving interleukin 2 and/or interferon alfa-2b therapy. *Journal of Clinical Oncology* 18(10): 2143–2151.
- Capuron L, Gunnick JF, Musselman DL, Lawson DH, Reemsnyder A, Nemeroff CB, Miller AH. 2002. Neurobehavioral effects of interferon-alpha in cancer patients: Phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology* 26(5):643–652.
- Carlsson GE, Moller A, Blomstrand C. 2003. Consequences of mild stroke in persons < 75 years—a 1-year follow-up. *Cerebrovascular Disease* 16(4):383–388.
- Carpenter JS, Johnson D, Wagner L, Andrykowski M. 2002. Hot flashes and related outcomes in breast cancer survivors and matched comparison women. *Oncological Nursing Forum* 29(3): E16–E25.
- Carskadon MA. 1990. Patterns of sleep and sleepiness in adolescents. *Pediatrician* 17(1):5–12.
- Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. 1986. Guidelines for the multiple sleep latency test (MSLT): A standard measure of sleepiness. *Sleep* 9(4):519–524.
- Carskadon MA, Acebo C, Jenni OG. 2004. Regulation of adolescent sleep: Implications for behavior. *Annals of the New York Academy of Sciences* 1021:276–291.

- CDC (Centers for Disease Control and Prevention). 2005. Percentage of adults who reported an average of ≤ 6 hours of sleep per 24-hour period, by sex and age group—United States, 1985 and 2004. *Morbidity and Mortality Weekly Report* 54(37):933.
- CDC. 2006. *Sudden Infant Death Syndrome (SIDS)*. [Online]. Available: <http://www.cdc.gov/SIDS/index.htm> [accessed January 17, 2006].
- Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ. 1997. Insomnia in young men and subsequent depression. The Johns Hopkins precursors study. *American Journal of Epidemiology* 146(2):105–114.
- Chen S, Ondo WG, Rao S, Li L, Chen Q, Wang Q. 2004. Genomewide linkage scan identifies a novel susceptibility locus for restless legs syndrome on chromosome 9p. *American Journal of Human Genetics* 74(5):876–885.
- Chervin RD, Archbold KH. 2001. Hyperactivity and polysomnographic findings in children evaluated for sleep-disordered breathing. *Sleep* 24(3):313–320.
- Chervin RD, Hedger AK, Dillon JE, Pituch KJ, Panahi P, Dahl RE, Guilleminault C. 2002. Associations between symptoms of inattention, hyperactivity, restless legs, and periodic leg movements. *Sleep: Journal of Sleep Research and Sleep Medicine* 25(2):213–218.
- Chin K, Nakamura T, Takahashi K, Sumi K, Ogawa Y, Masuzaki H, Muro S, Hattori N, Matsumoto H, Niimi A, Chiba T, Nakao K, Mishima M, Ohi M, Nakamura T. 2003. Effects of obstructive sleep apnea syndrome on serum aminotransferase levels in obese patients. *American Journal of Medicine* 114(5):370–376.
- Chrisp P, Mammen GJ, Sorkin EM. 1991. Selegiline. A review of its pharmacology, symptomatic benefits and protective potential in Parkinson's disease. *Drugs and Aging* 1(3):228–248.
- Cole MG, Dendukuri N. 2003. Risk factors for depression among elderly community subjects: A systematic review and meta-analysis. *American Journal of Psychiatry* 160(6):1147–1156.
- Coleman RM. 1982. Periodic movements in sleep (nocturnal myoclonus) and restless legs syndrome. In: Guilleminault C, ed. *Sleep and Waking Disorders: Indications and Techniques*. Menlo Park, CA: Addison-Wesley. Pp. 265–295.
- Comella CL, Nardine TM, Diederich NJ, Stebbins GT. 1998. Sleep-related violence, injury, and REM sleep behavior disorder in Parkinson's disease. *Neurology* 51(2):526–529.
- Connor JR, Boyer PJ, Menzies SL, Dellinger B, Allen RP, Ondo WG, Earley CJ. 2003. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. *Neurology* 61(3):304–309.
- Cronin AJ, Keifer JC, Davies MF, King TS, Bixler EO. 2001. Postoperative sleep disturbance: Influences of opioids and pain in humans. *Sleep* 24(1):39–44.
- Czeisler CA, Richardson GS, Zimmerman JC, Moore-Ede MC, Weitzman ED. 1981. Entrainment of human circadian rhythms by light-dark cycles: A reassessment. *Photochemistry and Photobiology* 34(2): 239–247.
- D'Alessandro R, Magelli C, Gamberini G, Bacchelli S, Cristina E, Magnani B, Lugaresi E. 1990. Snoring every night as a risk factor for myocardial infarction: A case-control study. *British Medical Journal* 300(6739):1557–1558.
- Daley KC. 2004. Update on sudden infant death syndrome. *Current Opinion in Pediatrics* 16(2):227–232.
- Dao TT, Lavigne GJ, Charbonneau A, Feine JS, Lund JP. 1994. The efficacy of oral splints in the treatment of myofascial pain of the jaw muscles: A controlled clinical trial. *Pain* 56(1):85–94.
- Darko DF, Mitler MM, Henriksen SJ. 1995. Lentiviral infection, immune response peptides and sleep. *Advances in Neuroimmunology* 5(1): 57–77.
- Dauvilliers Y, Touchon J. 2001. Sleep in fibromyalgia: Review of clinical and polysomnographic data [in French]. *Neurophysiologie Clinique* 31(1):18–33.

- Dauvilliers Y, Morin C, Cervena K, Carlander B, Touchon J, Besset A, Billiard M. 2005. Family studies in insomnia. *Journal of Psychosomatic Research* 58(3):271–278.
- Dawson D, Encel N. 1993. Melatonin and sleep in humans. *Journal of Pineal Research* 15(1): 1–12.
- de Rijk MC, Tzourio C, Breteler MM, Dartigues JF, Amaducci L, Lopez-Pousa S, Manubens-Bertran JM, Alperovitch A, Rocca WA. 1997. Prevalence of parkinsonism and Parkinson's disease in Europe: The EUROPARKINSON Collaborative Study. European Community Concerted Action on the Epidemiology of Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry* 62(1):10–15.
- Desautels A, Turecki G, Montplaisir J, Sequeira A, Verner A, Rouleau GA. 2001. Identification of a major susceptibility locus for restless legs syndrome on chromosome 12q. *American Journal of Human Genetics* 69(6):1266–1270.
- Diaz J, Sempere AP. 2004. Cerebral ischemia: New risk factors. *Cerebrovascular Disease* 17(suppl 1):43–50.
- Dinges DF, Pack F, Williams K, Gillen KA, Powell JW, Ott GE, Aptowicz C, Pack AI. 1997. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. *Sleep* 20(4):267–277.
- Dinges D, Ball E, Fredrickson P, Kiley J, Kryger MH, Richardson GS, Rogus S, Sheldon S, Wooten V, Zepf B. 1999. Recognizing problem sleepiness in your patients. *American Family Physician* 59(4):937–944.
- Dinges D, Rogers N, Baynard. 2005. Chronic sleep deprivation. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 67–76.
- Doherty LS, Kiely JL, Swan V, McNicholas WT. 2005. Long-term effects of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome. *Chest* 127(6):2076–2084.
- Drake CL, Roehrs T, Richardson G, Walsh JK, Roth T. 2004. Shift work sleep disorder: Prevalence and consequences beyond that of symptomatic day workers. *Sleep* 27(8):1453–1462.
- Dreifuss FE, Porter RJ. 1997. Choice of antiepileptic drugs. In: Engel J, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook*. Philadelphia: Lippincott-Raven. Pp. 1233–1236.
- Dunlop RJ, Campbell CW. 2000. Cytokines and advanced cancer. *Journal of Pain and Symptom Management* 20(3):214–232.
- Duran J, Esnaola S, Rubio R, Iztueta A. 2001. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *American Journal of Respiratory and Critical Care Medicine* 163(3):685–689.
- Dwyer T, Ponsonby AL, Newman NM, Gibbons LE. 1991. Prospective cohort study of prone sleeping position and sudden infant death syndrome. *Lancet* 337(8752):1244–1247.
- Dyken ME, Somers VK, Yamada T, Ren ZY, Zimmerman MB. 1996. Investigating the relationship between stroke and obstructive sleep apnea. *Stroke* 27(3):401–407.
- Eaker ED, Pinsky J, Castelli WP. 1992. Myocardial infarction and coronary death among women: Psychosocial predictors from a 20-year follow-up of women in the Framingham Study. *American Journal of Epidemiology* 135(8):854–864.
- Edinger JD, Means MK. 2005. Overview of insomnia: Definitions, epidemiology, differential diagnosis, and assessment. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 702–713.
- Ekblom KA. 1945. Restless legs. *Acta Medica Scandinavia Supplement* 158:1–123.
- Fantini ML, Gagnon JF, Filipini D, Montplaisir J. 2003. The effects of pramipexole in REM sleep behavior disorder. *Neurology* 61(10):1418–1420.
- Faulx MD, Larkin EK, Hoit BD, Aylor JE, Wright AT, Redline S. 2004. Sex influences endothelial function in sleep-disordered breathing. *Sleep* 27(6):1113–1120.

- Fava M. 2004. Daytime sleepiness and insomnia as correlates of depression. *Journal of Clinical Psychiatry* 65(suppl 16):27–32.
- Fawcett J, Scheftner WA, Fogg L, Clark DC, Young MA, Hedeker D, Gibbons R. 1990. Time-related predictors of suicide in major affective disorder. *American Journal of Psychiatry* 147(9):1189–1194.
- Ferguson KA, Lowe AA. 2005. Oral appliances for sleep-disordered breathing. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 1098–1108.
- Ferguson KA, Ono T, Lowe AA, Ryan CF, Fleetham JA. 1995. The relationship between obesity and craniofacial structure in obstructive sleep apnea. *Chest* 108(2):375–381.
- Fisher C, Byrne J, Edwards A, Kahn E. 1970. A psychophysiological study of nightmares. *Journal of American Psychoanalysis Association* 18(4):747–782.
- Foley DJ, Monjan AA, Brown SL, Simonsick EM, Wallace RB, Blazer DG. 1995. Sleep complaints among elderly persons: An epidemiologic study of three communities. *Sleep* 18(6):425–432.
- Foley DJ, Masaki K, White L, Larkin EK, Monjan A, Redline S. 2003. Sleep-disordered breathing and cognitive impairment in elderly Japanese-American men. *Sleep* 26(5):596–599.
- Folstein MF, Folstein SE, McHugh PR. 1975. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 12(3):189–198.
- Foo H, Mason P. 2003. Brainstem modulation of pain during sleep and waking. *Sleep Medicine Reviews* 7(2):145–154.
- Ford DE, Kamerow DB. 1989. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *Journal of the American Medical Association* 262(11):1479–1484.
- Fredriksen K, Rhodes J, Reddy R, Way N. 2004. Sleepless in Chicago: Tracking the effects of adolescent sleep loss during the middle school years. *Child Development* 75(1):84–95.
- Friedland RP, Brun A, Budinger TF. 1985. Pathological and positron emission tomographic correlations in Alzheimer’s disease. *Lancet* 1(8422):228.
- Gagnon JF, Bedard MA, Fantini ML, Petit D, Panisset M, Rompre S, Carrier J, Montplaisir J. 2002. REM sleep behavior disorder and REM sleep without atonia in Parkinson’s disease. *Neurology* 59(4):585–589.
- Gami AS, Howard DE, Olson EJ, Somers VK. 2005. Day-night pattern of sudden death in obstructive sleep apnea. *New England Journal of Medicine* 352(12):1206–1214.
- Garrick NA, Tamarkin L, Taylor PL, Markey SP, Murphy DL. 1983. Light and propranolol suppress the nocturnal elevation of serotonin in the cerebrospinal fluid of rhesus monkeys. *Science* 221(4609):474–476.
- Giles DE, Kupfer DJ, Rush AJ, Roffwarg HP. 1998. Controlled comparison of electrophysiological sleep in families of probands with unipolar depression. *American Journal of Psychiatry* 155(2):192–199.
- Gislason T, Benediktsdottir B. 1995. Snoring, apneic episodes, and nocturnal hypoxemia among children 6 months to 6 years old. An epidemiologic study of lower limit of prevalence. *Chest* 107(4):963–966.
- Good DC, Henkle JQ, Gelber D, Welsh J, Verhulst S. 1996. Sleep-disordered breathing and poor functional outcome after stroke. *Stroke* 27(2):252–259.
- Gottlieb DJ, Punjabi NM, Newman AB, Resnick HE, Redline S, Baldwin CM, Nieto FJ. 2005. Association of sleep time with diabetes mellitus and impaired glucose tolerance. *Archives of Internal Medicine* 165(8):863–867.
- Gronfier C, Wright KP Jr, Kronauer RE, Jewett ME, Czeisler CA. 2004. Efficacy of a single sequence of intermittent bright light pulses for delaying circadian phase in humans. *American Journal of Physiology—Endocrinology and Metabolism* 287(1):174–181.

- Grunstein R. 2005a. Continuous positive airway pressure treatment for obstructive sleep apnea-hypopnea syndrome. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 1066–1080.
- Grunstein R. 2005b. Endocrine disorders. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 1237–1245.
- Grunstein R, Wilcox I, Yang TS, Gould Y, Hedner J. 1993. Snoring and sleep apnoea in men: Association with central obesity and hypertension. *International Journal of Obesity-Related Metabolic Disorders* 17(9):533–540.
- Guilleminault C, Connolly SJ, Winkle RA. 1983. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. *American Journal of Cardiology* 52(5):490–494.
- Guilleminault C, Partinen M, Hollman K, Powell N, Stoohs R. 1995. Familial aggregates in obstructive sleep apnea syndrome. *Chest* 107(6):1545–1551.
- Gupta NK, Mueller WH, Chan W, Meininger JC. 2002. Is obesity associated with poor sleep quality in adolescents? *American Journal of Human Biology* 14(6):762–768.
- Hajak G, Muller WE, Wittchen HU, Pittrow D, Kirch W. 2003. Abuse and dependence potential for the non-benzodiazepine hypnotics Zolpidem and Zopiclone: A review of case reports and epidemiological data. *Addiction* 98(10):1371–1378.
- Halasz P, Ujaszasi J, Gadoros J. 1985. Are microarousals preceded by electroencephalographic slow wave synchronization precursors of confusional awakenings? *Sleep* 8(3):231–238.
- Haponik EF. 1992. Sleep disturbances of older persons: Physicians' attitudes. *Sleep* 15(2):168–172.
- Harma M, Tenkanen L, Sjoblom T, Alikoski T, Heinsalmi P. 1998. Combined effects of shift work and life-style on the prevalence of insomnia, sleep deprivation and daytime sleepiness. *Scandinavian Journal of Work, Environment and Health* 24(4):300–307.
- Harsch IA, Schahin SP, Radespiel-Troger M, Weintz O, Jahreiss H, Fuchs FS, Wiest GH, Hahn EG, Lohmann T, Konturek PC, Ficker JH. 2004. Continuous positive airway pressure treatment rapidly improves insulin sensitivity in patients with obstructive sleep apnea syndrome. *American Journal of Respiratory and Critical Care Medicine* 169(2):156–162.
- Harstall C, Ospina M. 2003. How prevalent is chronic pain? *Pain: Clinical Updates* 11(2): 1–4.
- Harvey AG. 2000. Sleep hygiene and sleep-onset insomnia. *Journal of Nervous and Mental Disease* 188(1):53–55.
- Hasler G, Buysse DJ, Klaghofer R, Gamma A, Ajdacic V, Eich D, Rossler W, Angst J. 2004. The association between short sleep duration and obesity in young adults: A 13-year prospective study. *Sleep* 27(4):661–666.
- Hasler G, Buysse DJ, Gamma A, Ajdacic V, Eich D, Rossler W, Angst J. 2005. Excessive daytime sleepiness in young adults: A 20-year prospective community study. *Journal of Clinical Psychiatry* 66(4):521–529.
- Hauck FR, Kemp JS. 1998. Bedsharing promotes breastfeeding and AAP Task Force on Infant Positioning and SIDS. *Pediatrics* 102(3 Pt 1):662–664.
- Hauck FR, Herman SM, Donovan M, Iyasu S, Merrick MC, Donoghue E, Kirschner RH, Willinger M. 2003. Sleep environment and the risk of sudden infant death syndrome in an urban population: The Chicago Infant Mortality Study. *Pediatrics* 111(5 Part 2): 1207–1214.
- Hauri PJ. 1997. Can we mix behavioral therapy with hypnotics when treating insomniacs? *Sleep* 20(12):1111–1118.
- He J, Kryger MH, Zorick FJ, Conway W, Roth T. 1988. Mortality and apnea index in obstructive sleep apnea. Experience in 385 male patients. *Chest* 94(1):9–14.

- Hening WA, Allen RP, Earley CJ, Picchiotti DL, Silber MH, Restless Legs Syndrome Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine. 2004. An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. *Sleep* 27(3):560–583.
- Hermida RC, Smolensky MH. 2004. Chronotherapy of hypertension. *Current Opinion in Nephrology and Hypertension* 13(5):501–505.
- Hilleman D, Miller MA, Parker R, Doering P, Pieper JA. 1998. Optimal management of amiodarone therapy: Efficacy and side effects. *Pharmacotherapy* 18(6 Pt 2):1385–1455.
- Hohagen F, Rink K, Kappler C, Schramm E, Riemann D, Weyerer S, Berger M. 1993. Prevalence and treatment of insomnia in general practice. A longitudinal study. *European Archives of Psychiatry and Clinical Neuroscience* 242(6):329–336.
- Hohjoh H, Takasu M, Shishikura K, Takahashi Y, Honda Y, Tokunaga K. 2003. Significant association of the arylalkylamine N-acetyltransferase (AA-NAT) gene with delayed sleep phase syndrome. *Neurogenetics* 4(3):151–153.
- Holmes MD, Chang M, Kapur V. 2003. Sleep apnea and excessive daytime somnolence induced by vagal nerve stimulation. *Neurology* 61(8):1126–1129.
- Hu FB, Willett WC, Manson JE, Colditz GA, Rimm EB, Speizer FE, Hennekens CH, Stampfer MJ. 2000. Snoring and risk of cardiovascular disease in women. *Journal of the American College of Cardiology* 35(2):308–313.
- Hublin C, Kaprio J, Partinen M, Heikkila K, Koskenvuo M. 1997. Prevalence and genetics of sleepwalking: A population-based twin study. *Neurology* 48(1):177–181.
- Hung J, Whitford EG, Parsons RW, Hillman DR. 1990. Association of sleep apnoea with myocardial infarction in men. *Lancet* 336(8710):261–264.
- Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. 2002. Obstructive sleep apnea is independently associated with insulin resistance. *American Journal of Respiratory and Critical Care Medicine* 165(5):670–676.
- Irgens LM, Markestad T, Baste V, Schreuder P, Skjaerven R, Oyen N. 1995. Sleeping position and sudden infant death syndrome in Norway 1967–91. *Archives of Disease in Childhood* 72(6):478–482.
- Iwase T, Kajimura N, Uchiyama M, Ebisawa T, Yoshimura K. 2002. Mutation screening of the human CLOCK gene in circadian rhythm sleep disorders. *Psychiatry Research* 109(2):121–128.
- Iyasu S, Randall LL, Welty TK, Hsia J, Kinney HC, Mandell F, McClain M, Randall B, Habbe D, Wilson H, Willinger M. 2002. Risk factors for sudden infant death syndrome among northern plains Indians. *Journal of the American Medical Association* 288(21):2717–2723.
- Janz D. 1962. The grand mal epilepsies and the sleeping-waking cycle. *Epilepsia* 3:69–109.
- Javaheri S, Parker TJ, Liming JD, Corbett WS, Nishiyama H, Wexler L, Roselle GA. 1998. Sleep apnea in 81 ambulatory male patients with stable heart failure: Types and their prevalences, consequences, and presentations. *Circulation* 97(21):2154–2159.
- Jeans WD, Fernando DC, Maw AR, Leighton BC. 1981. A longitudinal study of the growth of the nasopharynx and its contents in normal children. *British Journal of Radiology* 54(638):117–121.
- Jellinger K. 1986. Pathology of Parkinsonism. Fahn S, Marsden C, Goldstein M, Calne D, eds. *Recent Developments in Parkinson's Disease*. New York: Raven Press. Pp. 33–66.
- Jennum P, Hein HO, Suadicani P, Gyntelberg F. 1995. Risk of ischemic heart disease in self-reported snorers. A prospective study of 2,937 men aged 54 to 74 years: The Copenhagen male study. *Chest* 108(1):138–142.
- Johnson JG, Cohen P, Kasen S, First MB, Brook JS. 2004. Association between television viewing and sleep problems during adolescence and early adulthood. *Archives of Pediatrics and Adolescent Medicine* 158(6):562–568.

- Jones BE. 2005. Basic mechanisms of sleep-wake states. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 136–153.
- Jones CR, Campbell SS, Zone SE, Cooper F, DeSano A, Murphy PJ, Jones B, Czajkowski L, Ptacek LJ. 1999. Familial advanced sleep-phase syndrome: A short-period circadian rhythm variant in humans. *Nature Medicine* 5(9): 1062–1065.
- Juji T, Satake M, Honda Y, Doi Y. 1984. HLA antigens in Japanese patients with narcolepsy. All the patients were DR2 positive. *Tissue Antigens* 24(5):316–319.
- Kaakkola S. 2000. Clinical pharmacology, therapeutic use and potential of COMT inhibitors in Parkinson's disease. *Drugs* 59(6):1233–1250.
- Kales A, Ansel RD, Markham CH, Scharf MB, Tan TL. 1971. Sleep in patients with Parkinson's disease and normal subjects prior to and following levodopa administration. *Clinical Pharmacology and Therapeutics* 12(2):397–406.
- Kalra M, Inge T, Garcia V, Daniels S, Lawson L, Curti R, Cohen A, Amin R. 2005. Obstructive sleep apnea in extremely overweight adolescents undergoing bariatric surgery. *Obesity Research* 13(7):1175–1179.
- Kanbayashi T, Inoue Y, Chiba S, Aizawa R, Saito Y, Tsukamoto H, Fujii Y, Nishino S, Shimizu T. 2002. CSF hypocretin-1 (orexin-A) concentrations in narcolepsy with and without cataplexy and idiopathic hypersomnia. *Journal of Sleep Research* 11(1):91–93.
- Kaplan J, Fredrickson PA, Renaux SA, O'Brien PC. 1993. Theophylline effect on sleep in normal subjects. *Chest* 103(1):193–195.
- Kapsimalis F, Kryger MH. 2002. Gender and obstructive sleep apnea syndrome, part 1: Clinical features. *Sleep* 25(4):412–419.
- Kapur VK, Redline S, Nieto F, Young TB, Newman AB, Henderson JA. 2002. The relationship between chronically disrupted sleep and healthcare use. *Sleep* 25(3):289–296.
- Katz DA, McHorney CA. 1998. Clinical correlates of insomnia in patients with chronic illness. *Archives of Internal Medicine* 158(10):1099–1107.
- Katz I, Stradling J, Slutsky AS, Zamel N, Hoffstein V. 1990. Do patients with obstructive sleep apnea have thick necks? *American Review of Respiratory Disease* 141(5 Pt 1):1228–1231.
- Keech AC, Armitage JM, Wallendszus KR, Lawson A, Hauer AJ, Parish SE, Collins R. 1996. Absence of effects of prolonged simvastatin therapy on nocturnal sleep in a large randomized placebo-controlled study. Oxford Cholesterol Study Group. *British Journal of Clinical Pharmacology* 42(4):483–490.
- Kemp JS, Thach BT. 1991. Sudden death in infants sleeping on polystyrene-filled cushions. *New England Journal of Medicine* 324(26):1858–1864.
- Kinney HC, Filiano JJ, Sleeper LA, Mandell F, Valdes-Dapena M, White WF. 1995. Decreased muscarinic receptor binding in the arcuate nucleus in sudden infant death syndrome. *Science* 269(5229):1446–1450.
- Klackenberg G. 1982. Somnambulism in childhood—prevalence, course and behavioral correlations. A prospective longitudinal study (6–16 years). *Acta Paediatrica Scandinavia* 71(3):495–499.
- Kleitman N. 1987. *Sleep and Wakefulness*. Chicago: University of Chicago Press.
- Klerman EB, Dijk DJ. 2005. Interindividual variation in sleep duration and its association with sleep debt in young adults. *Sleep* 28(10):1253–1259.
- Konsman JP, Parnet P, Dantzer R. 2002. Cytokine-induced sickness behaviour: Mechanisms and implications. *Trends in Neuroscience* 25(3):154–159.
- Krahn LE. 2005. Psychiatric disorders associated with disturbed sleep. *Seminars in Neurology* 25(1):90–96.
- Krahn LE, Pankratz VS, Oliver L, Boeve BF, Silber MH. 2002. Hypocretin (orexin) levels in cerebrospinal fluid of patients with narcolepsy: Relationship to cataplexy and HLA DQB1*0602 status. *Sleep* 25(7):733–736.

- Kripke DF, Ancoli-Israel S, Klauber MR, Wingard DL, Mason WJ, Mullaney DJ. 1997. Prevalence of sleep-disordered breathing in ages 40-64 years: A population-based survey. *Sleep* 20(1):65-76.
- Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. 2002. Mortality associated with sleep duration and insomnia. *Archives in General Psychiatry* 59(2):131-136.
- Kryger MH, Otake K, Foerster J. 2002. Low body stores of iron and restless legs syndrome: A correctable cause of insomnia in adolescents and teenagers. *Sleep Medicine* 3(2):127-132.
- Kryger MH, Sheperdycky M, Foerster J, Manfreda J. 2003. Sleep disorders in repeat blood donors. *Sleep* 26(5):625-626.
- Kshatri AM, Baghdoyan HA, Lydic R. 1998. Cholinomimetics, but not morphine, increase antinociceptive behavior from pontine reticular regions regulating rapid-eye-movement sleep. *Sleep* 21(7):677-685.
- Lake CR, Rosenberg DB, Gallant S, Zaloga G, Chernow B. 1990. Phenylpropanolamine increases plasma caffeine levels. *Clinical Pharmacology and Therapeutics* 47(6):675-685.
- Lammers GJ, Overeem S. 2003. Pharmacological management of narcolepsy. *Expert Opinions in Pharmacotherapy* 4(10):1739-1746.
- Larkin EK, Rosen CL, Kirchner HL, Storfer-Isser A, Emancipator JL, Johnson NL, Zambito AM, Tracy RP, Jenny NS, Redline S. 2005. Variation of C-reactive protein levels in adolescents: Association with sleep-disordered breathing and sleep duration. *Circulation* 111(15):1978-1984.
- Lavie P, Lavie L, Herer P. 2005. All-cause mortality in males with sleep apnoea syndrome: Declining mortality rates with age. *European Respiratory Journal* 25(3):514-520.
- Lavigne GJ, Montplaisir JY. 1994. Restless legs syndrome and sleep bruxism: Prevalence and association among Canadians. *Sleep* 17(8):739-743.
- Lavigne GL, McMillan D, Zucconi M. 2005. Pain and sleep. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier Saunders. Pp. 1246-1255.
- Lee KA, Zaffke ME, Baratte-Beebe K. 2001. Restless legs syndrome and sleep disturbance during pregnancy: The role of folate and iron. *Journal of Women's Health and Gender-based Medicine* 10(4):335-341.
- Lee KA, Landis C, Chasens ER, Dowling G, Merritt S, Parker KP, Redeker N, Richards KC, Rogers AE, Shaver JF, Umlauf MG, Weaver TE. 2004. Sleep and chronobiology: Recommendations for nursing education. *Nursing Outlook* 52(3):126-133.
- Leeman AL, O'Neill CJ, Nicholson PW, Deshmukh AA, Denham MJ, Royston JP, Dobbs RJ, Dobbs SM. 1987. Parkinson's disease in the elderly: Response to and optimal spacing of night time dosing with levodopa. *British Journal of Clinical Pharmacology* 24(5):637-643.
- Levi F. 1994. Chronotherapy of cancer: Biological basis and clinical application [in French]. *Pathologie-Biologie (Paris)* 42(4):338-341.
- Lewy AJ, Ahmed S, Sack RL. 1996. Phase shifting the human circadian clock using melatonin. *Behavioural Brain Research* 73(1-2):131-134.
- Li KK, Kushida C, Powell NB, Riley RW, Guilleminault C. 2000. Obstructive sleep apnea syndrome: A comparison between Far-East Asian and white men. *Laryngoscope* 110(10 Pt 1):1689-1693.
- Lindberg E, Janson C, Svardsudd K, Gislason T, Hetta J, Boman G. 1998. Increased mortality among sleepy snorers: A prospective population-based study. *Thorax* 53(8):631-637.
- Lingjaerde O, Bratlid T, Hansen T. 1985. Insomnia during the "dark period" in northern Norway. An explorative, controlled trial with light treatment. *Acta Psychiatrica Scandinavia* 71(5):506-512.
- Liu X. 2004. Sleep and adolescent suicidal behavior. *Sleep* 27(7):1351-1358.
- Liu X, Uchiyama M, Kim K, Okawa M, Shibui K, Kudo Y, Doi Y, Minowa M, Ogihara R. 2000. Sleep loss and daytime sleepiness in the general adult population of Japan. *Psychiatry Research* 93(1):1-11.

- Liu Y, Tanaka H, Fukuoka Heart Study Group. 2002. Overtime work, insufficient sleep, and risk of non-fatal acute myocardial infarction in Japanese men. *Occupational and Environmental Medicine* 59(7):447–451.
- Livingston G, Blizzard B, Mann A. 1993. Does sleep disturbance predict depression in elderly people? A study in inner London. *British Journal of General Practice* 43(376): 445–448.
- Locard E, Mamelle N, Billette A, Miginiac M, Munoz F, Rey S. 1992. Risk factors of obesity in a five-year-old population: Parental versus environmental factors. *International Journal of Obesity and Related Metabolic Disorders* 16(10):721–729.
- Lundkvist GB, Kristensson K, Bentivoglio M. 2004. Why trypanosomes cause sleeping sickness. *Physiology (Bethesda)* 19(4):198–206.
- Mahowald MW, Ettinger MG. 1990. Things that go bump in the night: The parasomnias revisited. *Journal of Clinical Neurophysiology* 7(1):119–143.
- Mahowald MW, Schenck CH. 2005. Insights from studying human sleep disorders. *Nature* 437(7063):1279–1285.
- Malloy MH, Hoffman HJ. 1995. Prematurity, sudden infant death syndrome, and age of death. *Pediatrics* 96(3 Pt 1):464–471.
- Marcus CL, Greene MG, Carroll JL. 1998. Blood pressure in children with obstructive sleep apnea. *American Journal of Respiratory and Critical Care Medicine* 157(4 Pt 1):1098–1103.
- Marcus CL, Chapman D, Ward SD, McColley SA, Herrerias CT, Stillwell PC, Howenstine M, Light MJ, McColley SA, Schaeffer DA, Wagener JS, Laskosz LN. 2002. Clinical practice guideline: Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics* 109(4):704–712.
- Marin JM, Carrizo SJ, Vicente E, Agusti AG. 2005. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: An observational study. *Lancet* 365(9464):1046–1053.
- Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR. 1992. Role of glucose and insulin resistance in development of type 2 diabetes mellitus: Results of a 25-year follow-up study. *Lancet* 340(8825):925–929.
- McAinsh J, Cruickshank JM. 1990. Beta-blockers and central nervous system side effects. *Pharmacology and Therapeutics* 46(2):163–197.
- McArdle N, Riha RL, Vennelle M, Coleman EL, Dennis MS, Warlow CP, Douglas NJ. 2003. Sleep-disordered breathing as a risk factor for cerebrovascular disease: A case-control study in patients with transient ischemic attacks. *Stroke* 34(12):2916–2921.
- McClusky HY, Milby JB, Switzer PK, Williams V, Wooten V. 1991. Efficacy of behavioral versus triazolam treatment in persistent sleep-onset insomnia. *American Journal of Psychiatry* 148(1):121–126.
- McCracken LM, Iverson GL. 2002. Disrupted sleep patterns and daily functioning in patients with chronic pain. *Pain Research and Management: The Journal of the Canadian Pain Society* 7(2):75–79.
- Meier-Ewert HK, Ridker PM, Rifai N, Regan MM, Price NJ, Dinges DF, Mullington JM. 2004. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *Journal of the American College of Cardiologists* 43(4):678–683.
- Mellinger GD, Balter MB, Uhlenhuth EH. 1985. Insomnia and its treatment: Prevalence and correlates. *Archives of General Psychiatry* 42(3):225–232.
- Meny RG, Carroll JL, Carbone MT, Kelly DH. 1994. Cardiorespiratory recordings from infants dying suddenly and unexpectedly at home. *Pediatrics* 93(1):44–49.
- Miaskowski C, Lee KA. 1999. Pain, fatigue, and sleep disturbances in oncology outpatients receiving radiation therapy for bone metastasis: A pilot study. *Journal of Pain and Symptom Management* 17(5):320–332.

- Michaud M, Chabli A, Lavigne G, Montplaisir J. 2000. Arm restlessness in patients with restless legs syndrome. *Movement Disorders* 15(2):289–293.
- Mignot E. 1998. Genetic and familial aspects of narcolepsy. *Neurology* 50(2 suppl 1):S16–S22.
- Mignot E. 2001. A hundred years of narcolepsy research. *Archives of Italian Biology* 139(3): 207–220.
- Mignot E, Renaud A, Nishino S, Arrigoni J, Guilleminault C, Dement WC. 1993. Canine cataplexy is preferentially controlled by adrenergic mechanisms: Evidence using monoamine selective uptake inhibitors and release enhancers. *Psychopharmacology (Berlin)* 113(1):76–82.
- Mignot E, Lammers GJ, Ripley B, Okun M, Nevsimalova S, Overeem S, Vankova J, Black J, Harsh J, Bassetti C, Schrader H, Nishino S. 2002a. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. *Archives of Neurology* 59(10):1553–1562.
- Mignot E, Taheri S, Nishino S. 2002b. Sleeping with the hypothalamus: Emerging therapeutic targets for sleep disorders. *Nature Neuroscience* 5(suppl):1071–1075.
- Mitler MM, O'Malley MB. 2005. Wake-promoting medications: Efficacy and adverse effects. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 484–498.
- Miyazaki S, Uchida S, Mukai J, Nishihara K. 2004. Clonidine effects on all-night human sleep: Opposite action of low- and medium-dose clonidine on human NREM-REM sleep proportion. *Psychiatry and Clinical Neuroscience* 58(2):138–144.
- Moldofsky H. 2001. Sleep and pain. *Sleep Medicine Reviews* 5(5):385–396.
- Mondini S, Guilleminault C. 1985. Abnormal breathing patterns during sleep in diabetes. *Annals of Neurology* 17(4):391–395.
- Monk TH. 2005. Shift work: Basic principles. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 673–679.
- Monti JM, Hawkins M, Jantos H, D'Angelo L, Fernandez M. 1988. Biphasic effects of dopamine D-2 receptor agonists on sleep and wakefulness in the rat. *Psychopharmacology (Berlin)* 95(3):395–400.
- Montplaisir J, Petit D, Lorrain D, Gauthier S, Nielsen T. 1995. Sleep in Alzheimer's disease: Further considerations on the role of brainstem and forebrain cholinergic populations in sleep-wake mechanisms. *Sleep* 18(3):145–148.
- Montplaisir J, Petit D, McNamara D, Gauthier S. 1996. Comparisons between SPECT and quantitative EEG measures of cortical impairment in mild to moderate Alzheimer's disease. *European Neurology* 36(4):197–200.
- Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lesperance P. 1997. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: A study of 133 patients diagnosed with new standard criteria. *Movement Disorders* 12(1):61–65.
- Montplaisir J, Allen RP, Walters AD, Lerini-Strambi L. 2005. Restless legs syndrome and periodic limb movements during sleep. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 839–852.
- Moore T, Rabben T, Wiklund U, Franklin KA, Eriksson P. 1996a. Sleep-disordered breathing in men with coronary artery disease. *Chest* 109(3):659–663.
- Moore T, Rabben T, Wiklund U, Franklin KA, Eriksson P. 1996b. Sleep-disordered breathing in women: Occurrence and association with coronary artery disease. *American Journal of Medicine* 101(3):251–256.
- Moran M, Lynch CA, Walsh C, Coen R, Coakley D, Lawlor BA. 2005. Sleep disturbance in mild to moderate Alzheimer's disease. *Sleep Medicine* 6(4):347–352.

- Morin CM. 2005. Psychological and behavioral treatments for primary insomnia. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 726–737.
- Morin CM, Gibson D, Wade J. 1998. Self-reported sleep and mood disturbance in chronic pain patients. *Clinical Journal of Pain* 14(4):311–314.
- Morin CM, Mimeault V, Gagne A. 1999. Nonpharmacological treatment of late-life insomnia. *Journal of Psychosomatic Research* 46(2):103–116.
- Morrell MJ, Heywood P, Moosavi SH, Guz A, Stevens J. 1999. Unilateral focal lesions in the rostralateral medulla influence chemosensitivity and breathing measured during wakefulness, sleep, and exercise. *Journal of Neurology, Neurosurgery, and Psychiatry* 67(5):637–645.
- Morrison DN, McGee R, Stanton WR. 1992. Sleep problems in adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry* 31(1):94–99.
- Morton S, Rosen C, Larkin E, Tishler P, Aylor J, Redline S. 2001. Predictors of sleep-disordered breathing in children with a history of tonsillectomy and/or adenoidectomy. *Sleep* 24(7):823–829.
- Moser NJ, Phillips BA, Berry DT, Harbison L. 1994. What is hypopnea, anyway? *Chest* 105(2):426–428.
- Mourits MJ, De Vries EG, Willemse PH, Ten Hoor KA, Hollema H, Van der Zee AG. 2001. Tamoxifen treatment and gynecologic side effects: A review. *Obstetrics and Gynecology* 97(5 Pt 2):855–866.
- Murdey ID, Cameron N, Biddle SJ, Marshall SJ, Gorely T. 2005. Short-term changes in sedentary behaviour during adolescence: Project STIL (Sedentary Teenagers and Inactive Lifestyles). *Annals of Human Biology* 32(3):283–296.
- Murphy PJ, Badia P, Myers BL, Boecker MR, Wright KP Jr. 1994. Nonsteroidal anti-inflammatory drugs affect normal sleep patterns in humans. *Physiology and Behavior* 55(6):1063–1066.
- Murphy PJ, Myers BL, Badia P. 1996. Nonsteroidal anti-inflammatory drugs alter body temperature and suppress melatonin in humans. *Physiology and Behavior* 59(1):133–139.
- Namen AM, Wymer A, Case D, Haponik EF. 1999. Performance of sleep histories in an ambulatory medicine clinic: Impact of simple chart reminders. *Chest* 116(6):1558–1563.
- Namen AM, Landry SH, Case LD, McCall WV, Dunagan DP, Haponik EF. 2001. Sleep histories are seldom documented on a general medical service. *Southern Medical Journal* 94(9):874–879.
- Narkiewicz K, Somers VK. 2003. Sympathetic nerve activity in obstructive sleep apnoea. *Acta Physiologica Scandinavica* 177(3):385–390.
- Narkiewicz K, Kato M, Phillips BG, Pesek CA, Davison DE, Somers VK. 1999. Nocturnal continuous positive airway pressure decreases daytime sympathetic traffic in obstructive sleep apnea. *Circulation* 100(23):2332–2335.
- Netzer NC, Hoegel JJ, Loube D, Netzer CM, Hay B, Alvarez-Sala R, Strohl KP, Sleep in Primary Care International Study Group. 2003. Prevalence of symptoms and risk of sleep apnea in primary care. *Chest* 124(4):1406–1414.
- Newman AB, Spiekerman CF, Enright P, Lefkowitz D, Manolio T, Reynolds CF, Robbins J. 2000. Daytime sleepiness predicts mortality and cardiovascular disease in older adults. The Cardiovascular Health Study Research Group. *Journal of the American Geriatric Society* 48(2):115–123.
- NHLBI (National Heart, Lung, and Blood Institute). 2003. *National Sleep Disorders Research Plan, 2003*. Bethesda, MD: National Institutes of Health.

- NICHHD (National Institute of Child Health and Human Development). 2006a. *Safe Sleep for Your Baby: Ten Ways to Reduce the Risk of Sudden Infant Death Syndrome (SIDS)*. [Online]. Available: http://www.nichd.nih.gov/sids/reduce_infant_risk.htm [accessed January 17, 2006].
- NICHHD. 2006b. *SIDS Facts*. [Online]. Available: www.nichd.nih.gov/sids/PART_II.pdf [accessed March 13, 2006].
- Nichols DA, Allen RP, Grauke JH, Brown JB, Rice ML, Hyde PR, Dement WC, Kushida CA. 2002. Restless legs syndrome symptoms in primary care: A prevalence study. *Archives of Internal Medicine* 163(18):2323–2329.
- Nielsen TA, Zadra A. 2000. Dreaming disorders. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 3rd ed. Philadelphia: Elsevier Saunders. Pp. 753–772.
- Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. 2000. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *Journal of the American Medical Association* 283(14):1829–1836.
- Nieto FJ, Herrington DM, Redline S, Benjamin EJ, Robbins JA. 2004. Sleep apnea and markers of vascular endothelial function in a large community sample of older adults. *American Journal of Respiratory and Critical Care Medicine* 169(3):354–360.
- NIH (National Institutes of Health). 2005. *NIH State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults* [Online]. Available: <http://consensus.nih.gov/2005/2005InsomniaSOS026html.htm> [accessed March 6, 2006].
- NINDS (National Institute of Neurological Disorders and Stroke). 2005. *Restless Legs Syndrome Fact Sheet*. [Online]. Available: http://www.ninds.nih.gov/disorders/restless_legs/detail_restless_legs.htm [accessed June 13, 2005].
- Nishino S, Mignot E. 1997. Pharmacological aspects of human and canine narcolepsy. *Progress in Neurobiology* 52(1):27–78.
- Nofzinger EA, Buysse DJ, Germain A, Carter CS, Luna B, Price JC, Meltzer CC, Miewald JM, Reynolds CF, and Kupfer DJ. 2004a. Increased activation of anterior paralimbic and executive cortex from waking to REM sleep in depression. *Archives of General Psychiatry* 61(7):695–702.
- Nofzinger EA, Buysse DJ, Germain A, Price JC, Miewald JM, and Kupfer DJ. 2004b. Functional neuroimaging evidence for hyperarousal in insomnia. *American Journal of Psychiatry* 161(11):2126–2128.
- Nofzinger EA, Buysse DJ, Germain A, Price JC, Meltzer CC, Miewald JM, Kupfer DJ. 2005. Alterations in regional cerebral glucose metabolism across waking and non-rapid eye movement sleep in depression. *Archives of General Psychiatry* 62(4):387–396.
- Norman SE, Chediak AD, Kiel M, Cohn MA. 1990. Sleep disturbances in HIV-infected homosexual men. *AIDS* 4(8):775–781.
- Nowell PD, Buysse DJ, Reynolds CF III, Hauri PJ, Roth T, Stepanski EJ, Thorpy MJ, Bixler E, Kales A, Manfredi RL, Vgontzas AN, Stapf DM, Houck PR, Kupfer DJ. 1997. Clinical factors contributing to the differential diagnosis of primary insomnia and insomnia related to mental disorders. *American Journal of Psychiatry* 154(10):1412–1416.
- NSF (National Sleep Foundation). 2000a. *2000 Omnibus Sleep in America Poll*. [Online]. Available: www.sleepfoundation.org/publications/2001poll.html [accessed May 25, 2005].
- NSF. 2005b. *2005 Sleep in America Poll*. [Online]. Available: http://www.sleepfoundation.org/_content/hottopics/2005_summary_of_findings.pdf [accessed June 7, 2005].
- NSF. 2005c. *Shift work: Coping*. [Online]. Available: <http://www.sleepfoundation.org/sleepdictionary/index.php?id=20&subsection=coping> [accessed June 7, 2005].

- Ohayon MM. 2002. Epidemiology of insomnia: What we know and what we still need to learn. *Sleep Medicine Reviews* 6(2):97–111.
- Ohayon MM, Roth T. 2003. Place of chronic insomnia in the course of depressive and anxiety disorders. *Journal of Psychiatric Research* 37(1):9–15.
- Ohayon MM, Caulet M, Guilleminault C. 1997. How a general population perceives its sleep and how this relates to the complaint of insomnia. *Sleep* 20(9):715–723.
- Ohayon MM, Guilleminault C, Priest RG. 1999. Night terrors, sleepwalking, and confusional arousals in the general population: Their frequency and relationship to other sleep and mental disorders. *Journal of Clinical Psychiatry* 60(4):268–277.
- Ohayon MM, Priest RG, Zulley J, Smirne S. 2000. The place of confusional arousals in sleep and mental disorders: Findings in a general population sample of 13,057 subjects. *Journal of Nervous Mental Disease* 188(6):340–348.
- Olson EJ, Boeve BF, Silber MH. 2000. Rapid eye movement sleep behaviour disorder: Demographic, clinical and laboratory findings in 93 cases. *Brain* 123 (Pt 2):331–339.
- Ondze B, Espa F, Ming LC, Chakkar B, Besset A, Billiard M. 2001. Advanced sleep phase syndrome [in French]. *Reviews of Neurology* 157(11 Pt 2):S130–S134.
- Opp MR, Toth LA. 2003. Neural-immune interactions in the regulation of sleep. *Frontiers of Bioscience* 8:d768–d779.
- Overeem S, Scammell TE, Lammers GJ. 2002. Hypocretin/orexin and sleep: Implications for the pathophysiology and diagnosis of narcolepsy. *Current Opinion in Neurology* 15(6):739–745.
- Ozminkowski R, Wang S, Trautman H, Orsini L. 2004. Estimating the cost burden of insomnia for health plans. *Journal of Managed Care Pharmacy* 10(5):467.
- Palm L, Anderson H, Elmqvist D, Blennow G. 1992. Daytime sleep tendency before and after discontinuation of antiepileptic drugs in preadolescent children with epilepsy. *Epilepsia* 33(4):687–691.
- Palmer CR, Kripke DF, Savage HC Jr, Cindrich LA, Loving RT, Elliott JA. 2003. Efficacy of enhanced evening light for advanced sleep phase syndrome. *Behavioral Sleep Medicine* 1(4):213–226.
- Palmer LJ, Buxbaum SG, Larkin E, Patel SR, Elston RC, Tishler PV, Redline S. 2003. A whole-genome scan for obstructive sleep apnea and obesity. *American Journal of Human Genetics* 72(2):340–350.
- Palmer LJ, Buxbaum SG, Larkin EK, Patel SR, Elston RC, Tishler PV, Redline S. 2004. Whole genome scan for obstructive sleep apnea and obesity in African-American families. *American Journal of Respiratory and Critical Care Medicine* 169(12):1314–1321.
- Panichi V, Migliori M, De Pietro S, Taccola D, Andreini B, Metelli MR, Giovannini L, Palla R. 2000. The link of biocompatibility to cytokine production. *Kidney International Supplement* 76(suppl):S96–S103.
- Panigraphy A, Filiano JJ, Sleep LA, Mandell F, Valdes-Dapena M, Krous HF, Rava LA, White WF, Kinney HC. 1997. Decreased kainate receptor binding in the arcuate nucleus of the sudden infant death syndrome. *Journal of Neuropathology and Experimental Neurology* 56(11):1253–1261.
- Parker KP. 2003. Sleep disturbances in dialysis patients. *Sleep Medicine Reviews* 7(2):131–143.
- Parker KP, Bliwise DL, Rye DB. 2000. Hemodialysis disrupts basic sleep regulatory mechanisms: Building hypotheses. *Nursing Research* 49(6):327–332.
- Parra O, Arboix A, Bechich S, Garcia-Eroles L, Montserrat JM, Lopez JA, Ballester E, Guerra JM, Sopena JJ. 2000. Time course of sleep-related breathing disorders in first-ever stroke or transient ischemic attack. *American Journal of Respiratory and Critical Care Medicine* 161(2):375–380.

- Partinen M, Hublin C. 2005. Epidemiology of sleep disorders. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 626–647.
- Patel SR, White DP, Malhotra A, Stanchina ML, Ayas NT. 2003. Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea: Results of a meta-analysis. *Archives of Internal Medicine* 163(5): 565–571.
- Patel SR, Ayas NT, Malhotra MR, White DP, Schernhammer ES, Speizer FE, Stampfer MJ, Hu FB. 2004. A prospective study of sleep duration and mortality risk in women. *Sleep* 27(3):440–444.
- Paus S, Brecht HM, Koster J, Seeger G, Klockgether T, Wullner U. 2003. Sleep attacks, daytime sleepiness, and dopamine agonists in Parkinson's disease. *Movement Disorders* 18(6):659–667.
- Paykel ES, Fleming R, Watson JP. 1982. Psychiatric side effects of antihypertensive drugs other than reserpine. *Journal of Clinical Psychopharmacology* 2(1):14–39.
- Pelayo R, Thorpy MJ, Govinsky P. 1988. Prevalence of delayed sleep phase syndrome among adolescents. *Sleep Research* 17:392.
- Peppard PE, Young T, Palta M, Skatrud J. 2000. Prospective study of the association between sleep-disordered breathing and hypertension. *New England Journal of Medicine* 342(19): 1378–1384.
- Pereira DS, Tufik S, Louzada FM, Benedito-Silva AA, Lopez AR, Lemos NA, Korczak AL, D'Almeida V, Pedrazzoli M. 2005. Association of the length polymorphism in the human Per3 gene with the delayed sleep-phase syndrome: Does latitude have an influence upon it? *Sleep* 28(1):29–32.
- Perlis ML, Smith MT, Pigeon WR. 2005. Etiology and pathophysiology of insomnia. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 714–725.
- Pertosa G, Grandaliano G, Gesualdo L, Schena FP. 2000. Clinical relevance of cytokine production in hemodialysis. *Kidney International Supplement* 76:S104–S111.
- Peters RW. 2005. Obstructive sleep apnea and cardiovascular disease. *Chest* 127(1):1–3.
- Petit D, Montplaisir J, Boeve B. 2005. Alzheimer's disease and other dementias. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 853–862.
- Peyron C, Faraco J, Rogers W, Ripley B, Overeem S. 2000. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nature Medicine* 6(9):991–997.
- Phillips BG, Hisel TM, Kato M, Pesek CA, Dyken ME, Narkiewicz K, Somers VK. 1999. Recent weight gain in patients with newly diagnosed obstructive sleep apnea. *Journal of Hypertension* 17(9):1297–1300.
- Phillips BG, Kato M, Narkiewicz K, Choe I, Somers VK. 2000. Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea. *American Journal of Physiology—Heart and Circulatory Physiology* 279(1): H234–H237.
- Phillips B, Hening W, Britz P, Mannino D. 2006. Prevalence and correlates of restless legs syndrome: 2 Results from the 2005 National Sleep Foundation poll. *Chest* 129(1): 76–80.
- Picchiatti DL, England SJ, Walters AS, Willis K, Verrico T. 1998. Periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. *Journal of Child Neurology* 13(12): 588–594.

- Picchiatti DL, Underwood DJ, Farris WA, Walters AS, Shah MM, Dahl RE, Trubnick LJ, Bertocci MA, Wagner M, Hening WA. 1999. Further studies on periodic limb movement disorder and restless legs syndrome in children with attention-deficit hyperactivity disorder. *Movement Disorders* 14(6):1000–1007.
- Pilcher JJ, Huffcutt AI. 1996. Effects of sleep deprivation on performance: A meta-analysis. *Sleep* 19(4):318–326.
- Pillar G, Lavie P. 1995. Assessment of the role of inheritance in sleep apnea syndrome. *American Journal of Respiratory and Critical Care Medicine* 151(3 Pt 1): 688–691.
- Piazza G, Corsini R, Provini F, Pierangeli G, Martinelli P, Montagna P, Lugaresi E, Cortelli P. 1997. REM sleep behavior disorders in multiple system atrophy. *Neurology* 48(4):1094–1097.
- Piazza G, Cortelli P, Montagna P, De Monte A, Corsini R, Contin M, Provini F, Pierangeli G, Lugaresi E. 1998. REM sleep behaviour disorder differentiates pure autonomic failure from multiple system atrophy with autonomic failure. *Journal of Neurology, Neurosurgery and Psychiatry* 64(5):683–685.
- Ponsonby AL, Dwyer T, Gibbons LE, Cochrane JA, Wang YG. 1993. Factors potentiating the risk of sudden infant death syndrome associated with the prone position. *New England Journal of Medicine* 329(6):377–382.
- Powell NB, Riley RW, Guilleminault C. 2005. Surgical management of sleep-disordered breathing. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 1081–1097.
- Prinz PN, Peskind ER, Vitaliano PP, Raskind MA, Eisdorfer C, Zemcuznikov N, Gerber CJ. 1982a. Changes in the sleep and waking EEGs of nondemented and demented elderly subjects. *Journal of the American Geriatrics Society* 30(2):86–93.
- Prinz PN, Vitaliano PP, Vitiello MV, Bokan J, Raskind M, Peskind E, Gerber C. 1982b. Sleep, EEG and mental function changes in senile dementia of the Alzheimer's type. *Neurobiology of Aging* 3(4):361–370.
- Punjabi NM, Beamer BA. 2005. Sleep apnea and metabolic dysfunction. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 1034–1042.
- Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL. 2002. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *American Journal of Respiratory and Critical Care Medicine* 165(5):677–682.
- Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE, Sleep Heart Health Study Investigators. 2004. Sleep-disordered breathing, glucose intolerance, and insulin resistance: The Sleep Heart Health Study. *American Journal of Epidemiology* 160(6):521–530.
- Qureshi AI, Giles WH, Croft JB, Bliwise DL. 1997. Habitual sleep patterns and risk for stroke and coronary heart disease: A 10-year follow-up from NHANES I. *Neurology* 48(4):904–911.
- Radomski MW, Buguet A, Bogui P, Doua F, Lonsdorfer A, Tapie P, Dumas M. 1994. Disruptions in the secretion of cortisol, prolactin, and certain cytokines in human African trypanosomiasis patients. *Bulletin de la Societe de Pathologie Exotique (Paris)* 87(5): 376–379.
- Raison CL, Miller AH. 2001. The neuroimmunology of stress and depression. *Seminars in Clinical Neuropsychiatry* 6(4):277–294.
- Rao U, Dahl RE, Ryan ND, Birmaher B, Williamson DE, Giles DE, Rao R, Kaufman J, Nelson B. 1996. The relationship between longitudinal clinical course and sleep and cortisol changes in adolescent depression. *Biological Psychiatry* 40(6):474–484.

- Redline S, Tishler PV, Tosteson TD, Williamson J, Kump K, Browner I, Ferrette V, Krejci P. 1995. The familial aggregation of obstructive sleep apnea. *American Journal of Respiratory and Critical Care Medicine* 151(3 Pt 1):682–687.
- Redline S, Tishler PV, Hans MG, Tosteson TD, Strohl KP, Spry K. 1997. Racial differences in sleep-disordered breathing in African-Americans and Caucasians. *American Journal of Respiratory and Critical Care Medicine* 155(1):186–192.
- Redline S, Tishler PV, Schluchter M, Aylor J, Clark K, Graham G. 1999. Risk factors for sleep-disordered breathing in children: Associations with obesity, race, and respiratory problems. *American Journal of Respiratory and Critical Care Medicine* 159(5):1527–1532.
- Redline S, Kapur VK, Sanders MH, Quan SF, Gottlieb DJ, Rapoport DM, Bonekat WH, Smith PL, Kiley JP, Iber C. 2000. Effects of varying approaches for identifying respiratory disturbances on sleep apnea assessment. *American Journal of Respiratory and Critical Care Medicine* 161(2 Pt 1):369–374.
- Regestein QR, Monk TH. 1995. Delayed sleep phase syndrome: A review of its clinical aspects. *American Journal of Psychiatry* 152(4):602–608.
- Reid JL. 1996. New therapeutic agents for hypertension. *British Journal of Clinical Pharmacology* 42(1):37–41.
- Reid KJ, Zee PC. 2005. Circadian disorders of the sleep-wake cycle. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 691–701.
- Reid KJ, Chang AM, Dubocovich ML, Turek FW, Takahashi JS, Zee PC. 2001. Familial advanced sleep phase syndrome. *Archives of Neurology* 58(7):1089–1094.
- Reynolds CF III, Kupfer DJ, Taska LS, Hoch CC, Spiker DG, Sewitch DE, Zimmer B, Marin RS, Nelson JP, Martin D, Morycz R. 1985. EEG sleep in elderly depressed, demented, and healthy subjects. *Biological Psychiatry* 20(4):431–442.
- Reynolds CF III, Frank E, Houck PR, Mazumdar S, Dew MA, Cornes C, Buysse DJ, Begley A, Kupfer DJ. 1997. Which elderly patients with remitted depression remain well with continued interpersonal psychotherapy after discontinuation of antidepressant medication? *American Journal of Psychiatry* 154(7):958–962.
- Riemann D, Voderholzer U. 2003. Primary insomnia: A risk factor to develop depression? *Journal of Affective Disorders* 76(1-3):255–259.
- Riley JL III, Benson MB, Gremillion HA, Myers CD, Robinson ME, Smith CL Jr, Waxenberg LB. 2001. Sleep disturbance in orofacial pain patients: Pain-related or emotional distress? *Cranio* 19(2):106–113.
- Rizzo P, Beelke M, De Carli F, Canovaro P, Nobili L, Robert A, Tanganelli P, Regesta G, Ferrillo F. 2003. Chronic vagus nerve stimulation improves alertness and reduces rapid eye movement sleep in patients affected by refractory epilepsy. *Sleep* 26(5):607–611.
- Robinson GV, Pepperell JC, Segal HC, Davies RJ, Stradling JR. 2004a. Circulating cardiovascular risk factors in obstructive sleep apnoea: Data from randomised controlled trials. *Thorax* 59(9):777–782.
- Robinson GV, Stradling JR, Davies RJ. 2004b. Sleep 6: Obstructive sleep apnoea/hypopnoea syndrome and hypertension. *Thorax* 59(12):1089–1094.
- Roizenblatt S, Moldofsky H, Benedetto-Silva AA, Tufik S. 2001. Alpha sleep characteristics in fibromyalgia. *Arthritis and Rheumatism* 44(1):222–230.
- Rombaux P, Hamoir M, Plouin-Gaudon I, Liistro G, Aubert G, Rodenstein D. 2000. Obstructive sleep apnea syndrome after reconstructive laryngectomy for glottic carcinoma. *European Archives of Otorhinolaryngology* 257(9):502–506.
- Rosen CL, D'Andrea L, Haddad GG. 1992. Adult criteria for obstructive sleep apnea do not identify children with serious obstruction. *American Review of Respiratory Diseases* 146(5 Pt 1):1231–1234.

- Rosen CL, Larkin EK, Kirchner HL, Emancipator JL, Bivins SF, Surovec SA, Martin RJ, Redline S. 2003. Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: Association with race and prematurity. *Journal of Pediatrics* 142(4):383-389.
- Rosenfeld MR, Eichen JG, Wade DF, Posner JB, Dalmau J. 2001. Molecular and clinical diversity in paraneoplastic immunity to Ma proteins. *Annals of Neurology* 50(3):339-348.
- Rosenthal NE, Joseph-Vanderpool JR, Levendosky AA, Johnston SH, Allen R, Kelly KA, Souetre E, Schultz PM, Starz KE. 1990. Phase-shifting effects of bright morning light as treatment for delayed sleep phase syndrome. *Sleep* 13(4):354-361.
- Roth B. 1976. Narcolepsy and hypersomnia: Review and classification of 642 personally observed cases. *Schweizer Archiv fur Neurologie, Neurochirurgie und Psychiatrie* 119(1):31-41.
- Roth T, Ancoli-Israel S. 1999. Daytime consequences and correlates of insomnia in the United States: Results of the 1991 National Sleep Foundation Survey. II. *Sleep* 22(suppl 2):S354-S358.
- Rothdach AJ, Trenkwalder C, Haberstock J, Keil U, Berger K. 2000. Prevalence and risk factors of RLS in an elderly population: The MEMO study. Memory and morbidity in Augsburg elderly. *Neurology* 54(5):1064-1068.
- Ryan ND, Puig-Antich J, Ambrosini P, Rabinovich H, Robinson D, Nelson B, Iyengar S, Twomey J. 1987. The clinical picture of major depression in children and adolescents. *Archives of General Psychiatry* 44(10):854-861.
- Salinsky MC, Oken BS, Binder LM. 1996. Assessment of drowsiness in epilepsy patients receiving chronic antiepileptic drug therapy. *Epilepsia* 37(2):181-187.
- Santhi N, Duffy JF, Horowitz TS, Czeisler CA. 2005. Scheduling of sleep/darkness affects the circadian phase of night shift workers. *Neuroscience Letters* 384(3):316-320.
- Satoh K, Mishima K, Inoue Y, Ebisawa T, Shimizu T. 2003. Two pedigrees of familial advanced sleep phase syndrome in Japan. *Sleep* 26(4):416-417.
- Scammell TE. 2003. The neurobiology, diagnosis, and treatment of narcolepsy. *Annals of Neurology* 53(2):154-166.
- Schechtman VL, Harper RK, Harper RM. 1995. Aberrant temporal patterning of slow-wave sleep in siblings of SIDS victims. *Electroencephalography and Clinical Neurophysiology* 94(2):95-102.
- Schenck C, Mahowald M. 1990. A polysomnographic neurologic, psychiatric and clinical outcome report on 70 consecutive cases with REM sleep behavior disorder (RBD): sustained clonazepam efficacy in 89.5% of 57 treated patients. *Cleveland Clinic Journal of Medicine* 57(10):10-24.
- Schenck CH, Hurwitz TD, Mahowald MW. 1993. Symposium: Normal and abnormal REM sleep regulation: REM sleep behaviour disorder: An update on a series of 96 patients and a review of the world literature. *Journal of Sleep Research* 2(4):224-231.
- Schmidt-Nowara WW, Coultas DB, Wiggins C, Skipper BE, Samet JM. 1990. Snoring in a Hispanic-American population. Risk factors and association with hypertension and other morbidity. *Archives of Internal Medicine* 150(3):597-601.
- Schoendorf KC, Kiely JL. 1992. Relationship of sudden infant death syndrome to maternal smoking during and after pregnancy. *Pediatrics* 90(6):905-908.
- Schwartz SW, Cornoni-Huntley J, Cole SR, Hays JC, Blazer DG, Schocken DD. 1998. Are sleep complaints an independent risk factor for myocardial infarction? *Annals of Epidemiology* 8(6):384-392.
- Sekine M, Yamagami T, Handa K, Saito T, Nanri S, Kawaminami K, Tokui N, Yoshida K, Kagamimori S. 2002. A dose-response relationship between short sleeping hours and childhood obesity: Results of the Toyama birth cohort study. *Child: Care, Health and Development* 28(2):163-170.

- Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Javier Nieto F, O'Connor GT, Boland LL, Schwartz JE, Samet JM. 2001. Sleep-disordered breathing and cardiovascular disease: Cross-sectional results of the Sleep Heart Health Study. *American Journal of Respiratory and Critical Care Medicine* 163(1):19–25.
- Shahar E, Redline S, Young T, Boland LL, Baldwin CM, Nieto FJ, O'Connor GT, Rapoport DM, Robbins JA. 2003. Hormone replacement therapy and sleep-disordered breathing. *American Journal of Respiratory and Critical Care Medicine* 167(9):1186–1192.
- Shamsuzzaman AS, Gersh BJ, Somers VK. 2003. Obstructive sleep apnea: Implications for cardiac and vascular disease. *Journal of the American Medical Association* 290(14):1906–1914.
- Shepertycky MR, Banno K, Kryger MH. 2005. Differences between men and women in the clinical presentation of patients diagnosed with obstructive sleep apnea syndrome. *Sleep* 28(3):309–314.
- Shiino Y, Nakajima S, Ozeki Y, Isono T, Yamada N. 2003. Mutation screening of the human period 2 gene in bipolar disorder. *Neuroscience Letters* 338(1):82–84.
- Shouse MN, Mahowald M. 2005. Epilepsy, sleep, and sleep disorders. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 863–878.
- Shouse MN, da Silva AM, Sammaritano M. 1996. Circadian rhythm, sleep, and epilepsy. *Journal of Clinical Neurophysiology* 13(1):32–50.
- Silber MH, Richardson JW. 2003. Multiple blood donations associated with iron deficiency in patients with restless legs syndrome. *Mayo Clinic Proceedings* 78(1):52–54.
- Simon GE, VonKorff M. 1997. Prevalence, burden, and treatment of insomnia in primary care. *American Journal of Psychiatry* 154(10):1417–1423.
- Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. 1999. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *American Journal of Respiratory and Critical Care Medicine* 160(4):1101–1106.
- Singh M, Drake C, Roehrs T, Koshorek G, Roth T. 2005. The prevalence of SOREMPs in the general population. *Sleep* 28(abstract suppl):A221.
- Smith A. 1992. Sleep, colds, and performance. In: Broughton RJ, Ogilvie R, eds. *Sleep Arousal and Performance*. Boston: Birkhauser.
- Smith MT, Perlis ML, Park A, Smith MS, Pennington J, Giles DE, Buysse DJ. 2002. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. *American Journal of Psychiatry* 159(1):5–11.
- Somers VK, Mark AL, Abboud FM 1988. Sympathetic activation by hypoxia and hypercapnia—implications for sleep apnea. *Clinical and Experimental Hypertension: Part A, Theory and Practice* 10(suppl 1):413–422.
- Somers VK, Dyken ME, Mark AL, Abboud FM. 1992. Parasympathetic hyperresponsiveness and bradyarrhythmias during apnoea in hypertension. *Clinical Autonomic Research* 2(3):171–176.
- Somers VK, Dyken ME, Clary MP, Abboud FM. 1995. Sympathetic neural mechanisms in obstructive sleep apnea. *Journal of Clinical Investigation* 96(4):1897–1904.
- Spiegel K, Leproult R, Van Cauter E. 1999. Impact of sleep debt on metabolic and endocrine function. *Lancet* 354(9188):1435–1439.
- Spiegel K, Tasali E, Penev P, Van Cauter E. 2004. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Annals of Internal Medicine* 141(11):846–850.
- Stiasny K, Wetter TC, Winkelmann J, Brandenburg U, Penzel T, Rubin M, Hundemer HP, Oertel WH, Trenkwalder C. 2001. Long-term effects of pergolide in the treatment of restless legs syndrome. *Neurology* 56(10):1399–1402.

- Strine TW, Chapman DP. 2005. Associations of frequent sleep insufficiency with health-related quality of life and health behaviors. *Sleep Medicine* 6(1):23–27.
- Strohl KP, Redline S. 1996. Recognition of obstructive sleep apnea. *American Journal of Respiratory and Critical Care Medicine* 154(2 Pt 1):279–289.
- Strollo PJ, Atwood CW Jr, Sanders MH. 2005. Medical therapy for obstructive sleep apnea-hypopnea syndrome. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 1053–1065.
- Sulit LG, Storfer-Isser A, Rosen CL, Kirchner HL, Redline S. 2005. Associations of obesity, sleep-disordered breathing, and wheezing in children. *American Journal of Respiratory and Critical Care Medicine* 171(6):659–664.
- Szymczak JT, Jasinska M, Pawlak E, Zwierzykowska M. 1993. Annual and weekly changes in the sleep-wake rhythm of school children. *Sleep* 16(5):433–435.
- Taasan VC, Block AJ, Boysen PG, Wynne JW. 1981. Alcohol increases sleep apnea and oxygen desaturation in asymptomatic men. *American Journal of Medicine* 71(2):240–245.
- Taheri S, Lin L, Austin D, Young T, Mignot E. 2004. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *Public Library of Science Medicine* 1(3):210–217.
- Takahashi Y, Hohjoh H, Matsuura K. 2000. Predisposing factors in delayed sleep phase syndrome. *Psychiatry and Clinical Neuroscience* 54(3):356–358.
- Tamakoshi A, Ohno Y, JACC Study Group. 2004. Self-reported sleep duration as a predictor of all-cause mortality: Results from the JACC study, Japan. *Sleep* 27(1):51–54.
- Tassinari CA, Mancia D, Bernardina BD, Gastaut H. 1972. *Pavor nocturnus* of non-epileptic nature in epileptic children. *Electroencephalography and Clinical Neurophysiology* 33(6):603–607.
- Terzano MG, Parrino L, Spaggiari MC. 1988. The cyclic alternating pattern sequences in the dynamic organization of sleep. *Electroencephalography and Clinical Neurophysiology* 69(5):437–447.
- Thannickal TC, Moore RY, Nienhuis R, Ramanathan L, Gulyani S, Aldrich M, Cornford M, Siegel JM. 2000. Reduced number of hypocretin neurons in human narcolepsy. *Neuron* 27(3):469–474.
- Thorpy MJ. 2005. Classification of sleep disorders. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 615–625.
- Tishler PV, Redline S, Ferrette V, Hans MG, Altose MD. 1996. The association of sudden unexpected infant death with obstructive sleep apnea. *American Journal of Respiratory and Critical Care Medicine* 153(6 Pt 1):1857–1863.
- Tochikubo O, Ikeda A, Miyajima E, Ishii M. 1996. Effects of insufficient sleep on blood pressure monitored by a new multibiomedical recorder. *Hypertension* 27(6):1318–1324.
- Toh KL, Jones CR, He Y, Eide EJ, Hinz WA, Virshup DM, Ptacek LJ, Fu YH. 2001. An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. *Science* 291(5506):1040–1043.
- Toth LA. 1999. Microbial modulation of sleep. In: Lydic R, Baghdoyan HA, eds. *Handbook of Behavioral State Control: Cellular and Molecular Mechanisms*. Boca Raton, FL: CRC Press.
- Toth LA, Opp MR. 2002. Infection and sleep. In: Lee CT, Sateia M, Carskadon M. *Sleep Medicine*. Philadelphia, PA: Hanley and Belfus.
- Tractenberg RE, Singer CM, Kaye JA. 2005. Symptoms of sleep disturbance in persons with Alzheimer's disease and normal elderly. *Journal of Sleep Research* 14(2):177–185.

- Trampus M, Ferri N, Monopoli A, Ongini E. 1991. The dopamine D1 receptor is involved in the regulation of REM sleep in the rat. *European Journal of Pharmacology* 194(2-3):189-194.
- Tune GS. 1968. Sleep and wakefulness in normal human adults. *British Medical Journal* 2(600):269-271.
- Turek FW, Joshi C, Kohsaka A, Lin E, Ivanova G, McDearmon E, Laposky A, Losee-Olson S, Easton A, Jensen DR, Eckel RH, Takahashi JS, Bass J. 2005. Obesity and metabolic syndrome in circadian Clock mutant mice. *Science* 308(5724):1043-1045.
- Turjanski N, Lees AJ, Brooks DJ. 1999. Striatal dopaminergic function in restless legs syndrome: 18F-dopa and 11C-raclopride PET studies. *Neurology* 52(5):932-937.
- Ulfberg J, Nystrom B. 2004. Restless legs syndrome in blood donors. *Sleep Medicine* 5(2):115-118.
- United States Census Bureau. 1990. *Time Leaving Home to Go to Work for the United States: 1990 Census*. [Online] Available: <http://www.census.gov/population/socdemof/journey/usdeptim.txt> [accessed March 7, 2006].
- Unruh ML, Levey AS, D'Ambrosio C, Fink NE, Powe NR, Meyer KB. 2004. Restless legs symptoms among incident dialysis patients: Association with lower quality of life and shorter survival. *American Journal of Kidney Diseases* 43(5):900-909.
- Van den Heuvel CJ, Reid KJ, Dawson D. 1997. Effect of atenolol on nocturnal sleep and temperature in young men: Reversal by pharmacological doses of melatonin. *Physiology and Behavior* 61(6):795-802.
- Vaziri ND, Oveisi F, Wierszbiezki M, Shaw V, Sporty LD. 1993. Serum melatonin and 6-sulfatoxymelatonin in end-stage renal disease: Effect of hemodialysis. *Artificial Organs* 17(9):764-769.
- Vaziri ND, Oveisi F, Reyes GA, Zhou XJ. 1996. Dysregulation of melatonin metabolism in chronic renal insufficiency: Role of erythropoietin-deficiency anemia. *Kidney International* 50(2):653-656.
- Veasey S, Rosen R, Barzansky B, Rosen I, Owens J. 2002. Sleep loss and fatigue in residency training: A reappraisal. *Journal of the American Medical Association* 288(9):1116-1124.
- Velasco M, Velasco F. 1982. Brain stem regulation of cortical and motor excitability: Effects on experimental and focal motor seizures. In: Sterman MB, Shouse MN, Passouant P, eds. *Sleep and Epilepsy*. New York: Academic Press. Pp. 53-61.
- Verrier RL, Josephson ME. 2005. Cardiac arrhythmogenesis during sleep: Mechanisms, diagnosis, and therapy. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 1171-1191.
- Vgontzas AN, Kales A. 1999. Sleep and its disorders. *Annual Review of Medicine* 50(1):387-400.
- Vgontzas AN, Tan TL, Bixler EO, Martin LF, Shubert D, Kales A. 1994. Sleep apnea and sleep disruption in obese patients. *Archives of Internal Medicine* 154(15):1705-1711.
- Vgontzas AN, Bixler EO, Lin HM, Prolo P, Mastorakos G, Vela-Bueno A, Kales A, Chrousos GP. 2001. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: Clinical implications. *Journal of Clinical Endocrinology and Metabolism* 86(8): 3787-3794.
- Vincent NK, Hameed H. 2003. Relation between adherence and outcome in the group treatment of insomnia. *Behavioral Sleep Medicine* 1(3):125-139.
- Vioque J, Torres A, Quiles J. 2000. Time spent watching television, sleep duration and obesity in adults living in Valencia, Spain. *International Journal of Obesity and Related Metabolic Disorders* 24(12):1683-1688.

- von Kries R, Toschke AM, Wurmser H, Sauerwald T, Koletzko B. 2002. Reduced risk for overweight and obesity in 5- and 6-y-old children by duration of sleep—a cross-sectional study. *International Journal of Obesity and Related Metabolic Disorders: Journal of the International Association for the Study of Obesity* 26(5):710–716.
- Walsh JK, Dement WC, Dinges DF. 2005. Sleep medicine, public policy, and public health. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 648–656.
- Walters AS, Hening WA, Kavey N, Chokroverty S, Gidro-Frank S. 1988. A double-blind randomized crossover trial of bromocriptine and placebo in restless legs syndrome. *Annals of Neurology* 24(3):455–458.
- Walters AS, Wagner ML, Hening WA, Grasing K, Mills R, Chokroverty S, Kavey N. 1993. Successful treatment of the idiopathic restless legs syndrome in a randomized double-blind trial of oxycodone versus placebo. *Sleep* 16(4):327–332.
- Walters AS, Hickey K, Maltzman J, Verrico T, Joseph D, Hening W, Wilson V, Chokroverty S. 1996. A questionnaire study of 138 patients with restless legs syndrome: The “night-walkers” survey. *Neurology* 46(1):92–95.
- Walters AS, Winkelmann J, Trenkwalder C, Fry JM, Kataria V, Wagner M, Sharma R, Hening W, Li L. 2001. Long-term follow-up on restless legs syndrome patients treated with opioids. *Movement Disorders* 16(6):1105–1109.
- Weisberg RB, Bruce SE, Machan JT, Kessler RC, Culpepper L, Keller MB. 2002. Non-psychiatric illness among primary care patients with trauma histories and posttraumatic stress disorder. *Psychiatry Services* 53(7): 848–854.
- Weissman MM, Greenwald S, Nino-Murcia G, Dement WC. 1997. The morbidity of insomnia uncomplicated by psychiatric disorders. *General Hospital Psychiatry* 19(4):245–250.
- Weitzman ED, Czeisler CA, Coleman RM, Spielman AJ, Zimmerman JC, Dement W, Richardson G, Pollak CP. 1981. Delayed sleep phase syndrome. A chronobiological disorder with sleep-onset insomnia. *Archives of General Psychiatry* 38(7):737–746.
- Wesensten NJ, Belenky G, Kautz MA, Thorne DR, Reichardt RM, Balkin TJ. 2002. Maintaining alertness and performance during sleep deprivation: Modafinil versus caffeine. *Psychopharmacology (Berlin)* 159(3):238–247.
- Wetter TC, Stiasny K, Winkelmann J, Buhlinger A, Brandenburg U, Penzel T, Medori R, Rubin M, Oertel WH, Trenkwalder C. 1999. A randomized controlled study of pergolide in patients with restless legs syndrome. *Neurology* 52(5):944–950.
- Weyerbrock A, Timmer J, Hohagen F, Berger M, Bauer J. 1996. Effects of light and chronotherapy on human circadian rhythms in delayed sleep phase syndrome: Cytokines, cortisol, growth hormone, and the sleep-wake cycle. *Biological Psychiatry* 40(8):794–797.
- White DP. 2005. Central sleep apnea. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 969–982.
- Whitehouse PJ, Price DL, Struble RG, Clark AW, Coyle JT, Delon MR. 1982. Alzheimer’s disease and senile dementia: Loss of neurons in the basal forebrain. *Science* 215(4537):1237–1239.
- Wills L, Garcia J. 2002. Parasomnias: Epidemiology and management. *CNS Drugs* 16(12):803–810.
- Winkelmann JW, Chertow GM, Lazarus JM. 1996. Restless legs syndrome in end-stage renal disease. *American Journal of Kidney Disease* 28(3):372–378.
- Winkelmann J, Schadrack J, Wetter TC, Zieglerberger W, Trenkwalder C. 2001. Opioid and dopamine antagonist drug challenges in untreated restless legs syndrome patients. *Sleep Medicine* 2(1):57–61.

- Winkelmann J, Muller-Myhsok B, Wittchen HU, Hock B, Prager M, Pfister H, Strohle A, Eisensehr I, Dichgans M, Gasser T, Trenkwalder C. 2002. Complex segregation analysis of restless legs syndrome provides evidence for an autosomal dominant mode of inheritance in early age at onset families. *Annals of Neurology* 52(3):297–302.
- Wisor JP, Nishino S, Sora I, Uhl GH, Mignot E, Edgar DM. 2001. Dopaminergic role in stimulant-induced wakefulness. *Journal of Neuroscience* 21(5):1787–1794.
- Wolfson AR, Carskadon MA. 1998. Sleep schedules and daytime functioning in adolescents. *Child Development* 69(4):875–887.
- Wolkowitz OM, Rubinow D, Doran AR, Breier A, Berrettini WH, Kling MA, Pickar D. 1990. Prednisone effects on neurochemistry and behavior. Preliminary findings. *Archives of General Psychiatry* 47(10):963–968.
- Xu Y, Padiath QS, Shapiro RE, Jones CR, Wu SC, Saigoh N, Saigoh K, Ptacek LJ, Fu YH. 2005. Functional consequences of a CK1delta mutation causing familial advanced sleep phase syndrome. *Nature* 434(7033):640–644.
- Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. 2005. Obstructive sleep apnea as a risk factor for stroke and death. *New England Journal of Medicine* 353(19):2034–2041.
- Young T, Javaheri S. 2005. Systemic and pulmonary hypertension in obstructive sleep apnea. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 1192–1202.
- Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. 1993. The occurrence of sleep-disordered breathing among middle-aged adults. *New England Journal of Medicine* 328(17):1230–1235.
- Young T, Blustein J, Finn L, Palta M. 1997a. Sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. *Sleep* 20(8):608–613.
- Young T, Evans L, Finn L, Palta M. 1997b. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep* 20(9):705–706.
- Young T, Peppard PE, Gottlieb DJ. 2002a. Epidemiology of obstructive sleep apnea: A population health perspective. *American Journal of Respiratory and Critical Care Medicine* 165(9):1217–1239.
- Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ, Walsleben JA, Finn L, Enright P, Samet JM, Sleep Heart Health Study Research Group. 2002b. Predictors of sleep-disordered breathing in community-dwelling adults: The Sleep Heart Health Study. *Archives of Internal Medicine* 162(8):893–900.
- Young T, Rabago D, Zgierska A, Austin D, Laurel F. 2003. Objective and subjective sleep quality in premenopausal, perimenopausal, and postmenopausal women in the Wisconsin Sleep Cohort Study. *Sleep* 26(6):667–672.
- Zadra AL, Nielsen TA, Donderi DC. 1998. Prevalence of auditory, olfactory, and gustatory experiences in home dreams. *Perceptual and Motor Skills* 87(3 Pt 1):819–826.
- Zeitzer JM, Dijk DJ, Kronauer R, Brown E, Czeisler C. 2000. Sensitivity of the human circadian pacemaker to nocturnal light: Melatonin phase resetting and suppression. *Journal of Physiology* 526 (Pt 3):695–702.
- Zucconi M, Oldani A, Ferini-Strambi L, Smirne S. 1995. Arousal fluctuations in non-rapid eye movement parasomnias: The role of cyclic alternating pattern as a measure of sleep instability. *Journal of Clinical Neurophysiology* 12(2):147–154.
- Zweig RM, Jankel WR, Hedreen JC, Mayeux R, Price DL. 1989. The pedunculopontine nucleus in Parkinson's disease. *Annals of Neurology* 26(1):41–44.

4

Functional and Economic Impact of Sleep Loss and Sleep-Related Disorders

CHAPTER SUMMARY *Sleep loss and sleep disorders affect an individual's performance, safety, and quality of life. Almost 20 percent of all serious car crash injuries in the general population are associated with driver sleepiness, independent of alcohol effects. Further, sleep loss and sleep disorders have a significant economic impact. The high estimated costs to society of leaving the most prevalent sleep disorders untreated are far more than the costs that would be incurred by delivering adequate treatment. Hundreds of billions of dollars a year are spent on direct medical costs associated with doctor visits, hospital services, prescriptions, and over-the-counter drugs. Compared to healthy individuals, individuals suffering from sleep loss, sleep disorders, or both are less productive, have an increased health care utilization, and an increased likelihood of accidents.*

The public health consequences of sleep loss, night work, and sleep disorders are far from benign. Some of the most devastating human and environmental health disasters have been partially attributed to sleep loss and night shift work-related performance failures, including the tragedy at the Bhopal, India, chemical plant; the nuclear reactor meltdowns at Three Mile Island and Chernobyl; as well as the grounding of the *Star Princess* cruise ship and the Exxon *Valdez* oil tanker (NCSDS, 1994; NTSB, 1997; Moss and Sills, 1981; United States Senate Committee on Energy and National Resources, 1986; USNRC, 1987; Dinges et al., 1989). Each of these incidents not only cost millions of dollars to clean up, but also had a significant impact on the environment and the health of local communities.

Less visible consequences of sleep conditions take a toll on nearly every key indicator of public health: mortality, morbidity, performance, accidents and injuries, functioning and quality of life, family well-being, and health care utilization. This chapter begins with an overview of the consequences of sleep loss and sleep disorders on an individual's performance, safety, and quality of life. Drawing on the available body of evidence, the chapter then describes the economic impact of sleep loss and sleep disorders.

PERFORMANCE AND COGNITION DEFICITS

Nearly all types of sleep problems are associated with performance deficits in occupational, educational, and other settings. The deficits include attention, vigilance, and other measures of cognition, including memory and complex decision making. This section addresses sleep loss and then turns to sleep-disordered breathing and other sleep disorders.

Sleep Loss Affects Cognitive Performance

Sleep loss had been largely dismissed as the cause of poor cognitive performance by early, yet poorly designed, research. The prevailing view until the 1990s was that people adapted to chronic sleep loss without adverse cognitive effects (Dinges et al., 2005). More recent research has revealed sleep loss-induced neurobehavioral effects, which often go unrecognized by the affected individuals. The neurobehavioral impact extends from simple measures of cognition (i.e., attention and reaction time) to far more complex errors in judgment and decision making, such as medical errors, discussed below and in Box 4-1. Performance effects of sleep loss include the following:

- Involuntary microsleeps occur.
- Attention to intensive performance is unstable, with increased errors of omission and commission.

BOX 4-1
**Reducing Interns' Work Hours in Intensive Care Units
Lowers Medical Errors**

The longstanding debate over medical residents' lengthy work hours pits patient safety advocates against those who view the practice as necessary for continuity of care, preparation for medical practice, and cost containment (Steinbrook, 2002). After years of debate, and the threat of federal regulations, the Accreditation Council for Graduate Medical Education changed its requirements in 2003 to restrict residents' work hours to about 80 hours per week (ACGME, 2003). The policy permits no more than a maximum shift duration of 24 hours and overnight call no more than every third night.

Does this revised policy protect patients? The Harvard Work Hours, Health and Safety Study compared a schedule of about 80 hours per week (termed the *traditional schedule*) with a reduced schedule that eliminated shifts of 24 hours or more and kept work hours under 63 per week. The trial was conducted in intensive care units because they typically have the longest hours and the highest rates of errors.

The intervention schedule not only enhanced interns' sleep duration and lowered their rate of attentional failures, but also reduced the rate of serious medical errors, according to two articles published in 2004 in the *New England Journal of Medicine*. In the first article, the investigators used a within-subjects design ($n = 20$ interns) and validated sleep duration by polysomnography and attentional failures by slow-rolling eye movements recorded during continuous electro-oculography. Under the intervention schedule, the article reported that residents slept nearly 6 more hours per week, and they experienced half the rate of attentional failures during on-call nights than under the traditional schedule (Lockley et al., 2004).

The second article on medical errors reported results after randomizing interns to either the traditional or reduced schedule (Landrigan et al., 2004). Two physicians who directly observed the interns without awareness of their schedules identified serious medical errors, defined as causing or having the potential to cause harm to a patient. Errors were recorded by type (medication, diagnosis, and procedure) and in terms of number, or rate per 1,000 patient days. The study covered a total of 2,203 patient-days involving 634 admissions. Under the traditional schedule, interns made nearly 21 percent more medication errors and at least five times more diagnostic errors. Overall, the unitwide rate of serious medical errors was 22 percent higher in the traditional versus the intervention schedule ($P < .001$) as shown in the table below. The investigators concluded that reducing interns' hours can lower the occurrence of serious medical errors in the intensive care unit.

continued

BOX 4-1 continued

Incidence of Serious Medical Errors (rate/1,000 patient days)

Variable	Traditional Schedule	Intervention Schedule	P Value
Serious medical errors made by interns			
Serious medical errors	176 (136.0)	91 (100.1)	< 0.001
Preventable adverse events	27 (20.9)	15 (16.5)	0.21
Intercepted serious errors	91 (70.3)	50 (55.0)	0.02
Nonintercepted serious errors	58 (44.8)	26 (28.6)	< 0.001
Types of serious medical errors made by interns			
Medication	129 (99.7)	75 (82.5)	0.03
Procedural	11 (8.5)	6 (6.6)	0.34
Diagnostic	24 (18.6)	3 (3.3)	< 0.001
Other	12 (9.3)	7 (7.7)	0.47
All serious medical errors, unitwide			
Serious medical errors	250 (193.2)	144 (158.4)	< 0.001
Preventable adverse events	50 (38.6)	35 (38.5)	0.91
Intercepted serious errors	123 (95.1)	63 (69.3)	< 0.001
Nonintercepted serious errors	77 (59.5)	46 (50.6)	0.14
Types of serious medical errors made by interns			
Medication	175 (135.2)	105 (115.5)	0.03
Procedural	18 (13.9)	11 (12.1)	0.48
Diagnostic	28 (21.6)	10 (11.0)	< 0.001
Other	29 (22.4)	18 (19.8)	0.45

SOURCE: Landrigan et al. (2004).

- Cognitive slowing occurs in subject-paced tasks, while time pressure increases cognitive errors.
- Response time slows.
- Performance declines in short-term recall of working memory.
- Performance requiring divergent thinking deteriorates.
- Learning (acquisition) of cognitive tasks is reduced.
- An increase in response suppression errors in tasks requiring normal primarily prefrontal cortex function.

- The likelihood of response preservation on ineffective solutions is increased.
- Compensatory efforts to remain behaviorally effective are increased.
- Although tasks may be done well, performance deteriorates as tasks duration increases (Durmer and Dinges, 2005).

Attention and reaction time are altered by experimental sleep loss, which leads to cumulative, dose-dependent deterioration of attention and reaction time (Figure 4-1). Deterioration is measured in part using the psy-

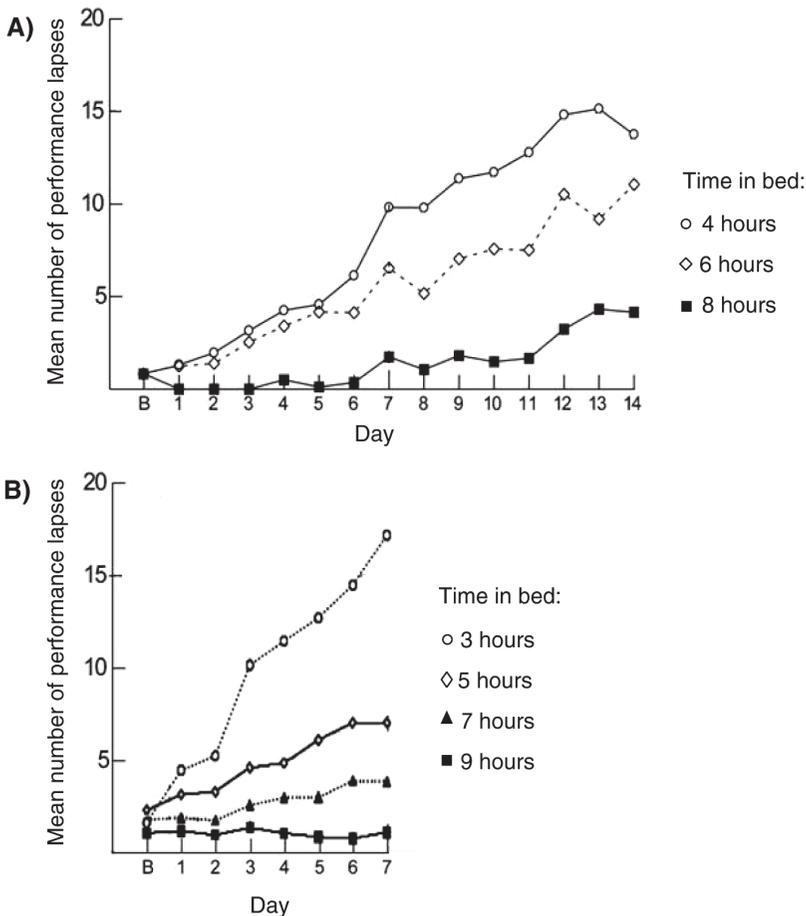


FIGURE 4-1 Repeated nights of sleep loss have cumulative cognitive impairment. NOTE: B, baseline day.

SOURCES: (A) Van Dongen et al. (2003); (B) Belenky et al. (2003).

chomotor vigilance task (PVT), a test that requires continuous attention to detect randomly occurring stimuli and that is impervious to aptitude and learning effects. In one study 48 healthy subjects were randomized to 4, 6, or 8 hours time in bed for 14 days (Van Dongen et al., 2003). Investigators found a dose-dependent effect, which increased over time (Figure 4-1A). Performance deficits in individuals who slept 6 hours or less per night were similar to those observed in individuals after two nights of *total* sleep deprivation. Most striking was that study subjects remained largely unaware of their performance deficits, as measured by subjective sleepiness ratings. A second study (Belenky et al., 2003) showed a similar dose-dependent, cumulative effect over 7 days of sleep loss in 66 healthy volunteers (Figure 4-1B). Subjects were followed for 3 days after the period of sleep restriction, during which time they recovered, but not enough to return to their baseline levels. Imaging studies have demonstrated a physiological basis for cognitive impairments with sleep loss that has been linked with metabolic declines in the frontal lobe of the brain (Thomas et al., 2000). Although there is not a large body of evidence, associations are also likely between sleep loss and increased risk taking (Roehrs et al., 2004).

Sleep Loss in Adolescents and Academic Performance

Sleep loss in adolescence is common and grows progressively worse over the course of adolescence, according to studies from numerous countries (Wolfson and Carskadon, 2003; Howell et al., 2004). Average sleep duration diminishes by 40 to 50 minutes from ages 13 to 19. Despite the physiological need for about 9 hours of sleep, sleep duration, across this age span, averages around 7 hours and about a quarter of high school and college students are sleep deprived (Wolfson and Carskadon, 1998). Research indicates that patterns of shortened sleep occur in the preadolescent period and may be most marked in African American boys, compared to white children or African American girls (Spilisbury et al., 2004). The decline in adolescent sleep duration is attributed to psychological and social changes, including growing desire for autonomy, increased academic demands, and growing social and recreational opportunities, all of which take place in spite of no change in rise time for school (Figure 4-2) (Wolfson and Carskadon, 1998). Furthermore, the need to earn income adds to the burden. Students who worked 20 or more hours weekly, compared with those who worked less than 20 hours, were found to go to bed later, sleep fewer hours, oversleep, and fall asleep more in class (Millman et al., 2005).

Sleep loss affects alertness, attention, and other cognitive functions in adolescents (Randazzo et al., 1998), but demonstrating a causal relationship between sleep loss and academic performance has been difficult. Most studies attempting to link the two are cross-sectional in design, based on

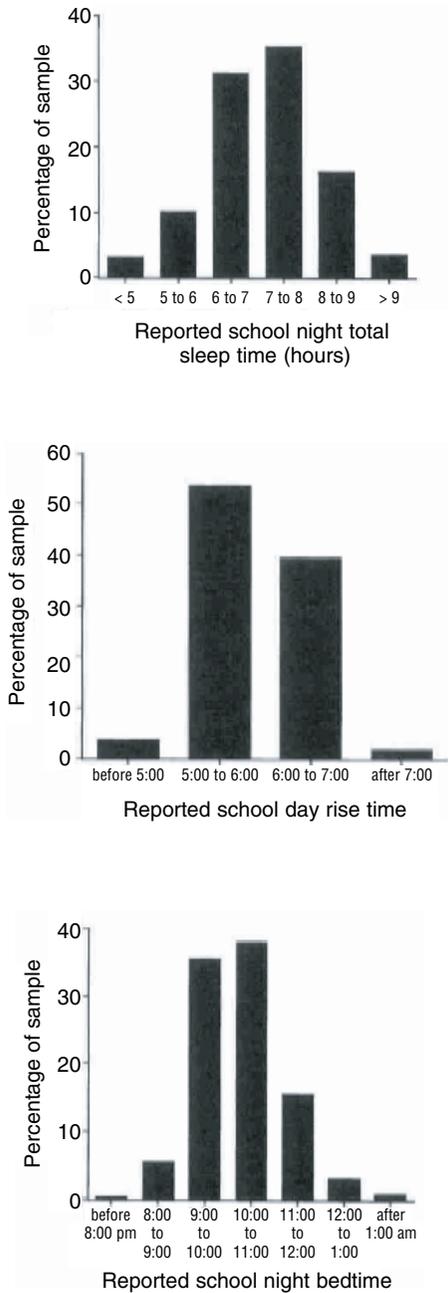


FIGURE 4-2 Sample distribution of sleep patterns.
SOURCE: Wolfson and Carskadon (1998).

self-reporting of grades and sleep times, and lack a control for potential confounders (Wolfson and Carskadon, 2003). An association between short sleep duration and lower academic performance has been demonstrated (Wolfson and Carskadon, 1998; Drake et al., 2003; Shin et al., 2003), but the question of causality has not been resolved by longitudinal studies. A 3-year study of 2,200 middle school students did not find that sleep loss resulted in lower academic performance. It only found a cross-sectional association at the beginning of the study. However, by the end of the study, as sleep time worsened, grades did not proportionately decrease (Fredriksen et al., 2004). A study of the Minneapolis School District, which delayed start times for its high schools by almost 1.5 hours (from 7:15 a.m. to 8:40 a.m.), found significant improvements in sleep time, attendance, and fewer symptoms of depressed mood (Wahlstrom et al., 2001). Further, there was a trend toward better grades, but not of statistical significance. The study compared grades over the 3 years prior to the change with grades 3 years afterwards.

Much of the difficulty in studying sleep loss and its relation to academic performance stems from multiple, often unmeasured, environmental factors that affect sleep (such as school demands, student employment after school, family influences, TV viewing, and Internet access). These are set against the rapid developmental and physiological changes occurring in adolescence. Another difficulty is the challenge of objectively assessing school performance (Wolfson and Carskadon, 2003).

Additional robust intervention studies are needed to determine the effect of having later school start times on student performance. However, a confounder to later school start times is the potential onset of sleep phase delay during middle school (seventh and eighth grade). Moving middle school start time early to compensate for later high school start time may be problematic for the middle school children. There have been no studies that have examined effects of early start time on elementary-aged children (Wolfson and Carskadon, 2003). An alternative to changing the school starting times might be to implement bright light therapy in early morning classes for high school students as a means to change the circadian timing system of these students and thereby enable earlier sleep schedules (Wolfson and Carskadon, 2003).

Sleep Loss and Medical Errors

The Institute of Medicine's report *To Err Is Human* estimated that as many as 98,000 deaths—due to medical errors—occur annually in United States hospitals (IOM, 2000). Long work hours and extended shifts among hospital workers are now known to contribute to the problem. Since the report's release, several new studies, discussed below, have found strong

relationships between sleep loss, shift duration, and medical errors among medical residents.

Medical residents work longer hours than virtually all other occupational groups (Steinbrook, 2002). During the first year, medical residents frequently work a 24-hour shift every third night (i.e., 96-hours per week). Two studies found that sleep-deprived surgical residents commit up to twice the number of errors in a simulated laparoscopic surgery (Grantcharov et al., 2001; Eastridge et al., 2003). In a survey of 5,600 medical residents, conducted by the Accreditation Council for Graduate Medical Education, total work time was inversely correlated with reported sleep time. Residents who worked more than 80 hours per week were 50 percent more likely than those working less than 80 hours to report making a significant medical error that led to an adverse patient outcome (Baldwin and Daugherty, 2004). The strongest evidence tying medical errors to sleep-related fatigue from extended work hours comes from an intervention trial designed to limit residents' work hours (Box 4-1). Earlier attempts to demonstrate patient safety benefits by reducing resident hours were beset by methodological problems (Fletcher et al., 2004).

Residents are not the only health professionals to report medical errors in association with short sleep. Nurses who completed logbooks recording their schedule length, sleep, and errors, reported 3.3 times more medical errors during 12.5 hour shifts than 8.5 hour shifts (Rogers et al., 2004). Nearly 40 percent of the nurses reported having 12-hour shifts; and although their sleep duration was not directly studied, the findings suggest that fatigue is a major factor.

Obstructive Sleep Apnea Is Associated with Development, Cognition, and Behavior in Children

Children with obstructive sleep apnea (OSA) often have problems in development, cognition, behavior, and academic performance, according to detailed reviews of the evidence (Schechter, 2002; Bass et al., 2004). The risk of neurobehavioral abnormalities in children with severe OSA is about three times greater than in children without OSA (Schechter, 2002). The contribution of overnight reduction of oxygen levels in the blood (hypoxemia) in comparison to sleep disruption is unclear. One study shows an association with the lowest level of oxygen during sleep and scores in arithmetic (Urschitz et al., 2005), but other studies show cognitive or behavioral deficits in children who snore without severe sleep apnea (Kennedy et al., 2004; Rosen et al., 2004; Gottlieb et al., 2004; O'Hara et al., 2005). Outcome measures used in numerous studies include intelligence quotient, learning and vocabulary, attention, symptoms of attention deficit hyperactivity disorder (ADHD), and academic performance. For example, two historical

cohort studies found decrements in intelligence quotient, impaired learning, and vocabulary in children with polysomnography-confirmed cases (Rhodes et al., 1995; Blunden et al., 2000). A study of younger children with sleep apnea also did not find a relationship with academic performance, after adjusting for the effects of socioeconomic status (Chervin et al., 2003). O'Brien and colleagues (2004) found that 35 children with sleep-disordered breathing, compared with matched controls, showed significant deficits in neurocognition, including overall cognitive ability, as well as attention and executive function, but the study did not find behavioral differences. A previous study by the same researchers found higher symptoms of ADHD, according to parents' reports, in children with OSA (O'Brien et al., 2003). Several other studies have found greater symptoms of ADHD in children with OSA than controls (Weissbluth and Liu, 1983; Stradling et al., 1990; Chervin et al., 1997).

The neurobehavioral effects of OSA may be partially reversible with tonsillectomy and adenoidectomy, a surgical procedure that opens the airway. Treatment is related to partial improvement in school performance, cognition, or behavior (Ali et al., 1996; Friedman et al., 2003). A limitation to this work is that it is often difficult to control for the many confounders that influence cognitive function, with a recent study showing that after robustly adjusting for neighborhood socioeconomic status (Emancipator et al., 2006), effects were much attenuated, although they persisted in a subgroup of children who had been born prematurely. No randomized controlled study has been conducted to address the potential reversibility of cognitive deficits with sleep-disordered breathing; such data would more definitively address this situation. Gozal (1998) studied 54 children with sleep-disordered breathing and low school performance. Half of them underwent surgical tonsillectomy and adenoidectomy to treat OSA. Children undergoing the interventions improved their academic performance, compared to untreated children. One problem with the study design; however, was that surgical treatment was not randomly assigned (parents elected whether or not their children could receive surgery). Given the high proportion of children with sleep-disordered breathing, especially in vulnerable groups such as children in minority populations and those born prematurely, there is a large need to address the role of sleep-disordered breathing and its reversibility in these important outcomes.

Sleep-Disordered Breathing and Cognitive Impairment in Adults

Several cross-sectional studies indicate that sleep-disordered breathing in adults is associated with impaired cognitive function (Greenberg et al., 1987; Bedard et al., 1991; Naegele et al., 1995; Redline et al., 1997; Kim et al., 1997). Cognitive deficits, in turn, partially contribute to poorer work

performance (Ulfberg et al., 1996), accidents and injuries, and deterioration of the quality of life (see later sections).

A meta-analysis of the case-control studies found that the magnitude of the cognitive disturbance was greatest in individuals with severe OSA. Cognitive domains most affected were attention and executive function (the capacity to plan and organize complex tasks) with only milder effects on memory (Engleman et al., 2000). The meta-analysis also found some cognitive benefit associated with continuous positive airway pressure (CPAP) treatment. In a series of randomized, placebo-controlled crossover trials, people with mild OSA exhibited a trend toward better performance. The failure to detect a robust effect may have been due to the fact that the patients had mild disease, were nonadherent to therapy, or that they had a possibly irreversible component to the cognitive impairment. The cognitive deficits with sleep-disordered breathing are thought to be related to both sleep fragmentation and hypoxemia (Weaver and George, 2005). However, one study showed no clear threshold level between level of hypoxia and performance deficits (Adams et al., 2001). Animal models of chronic episodic hypoxia have led to the hypothesis that cognitive deficits in humans result from injury of nerve cells in the prefrontal cortex (Beebe and Gozal, 2002), the area of the brain responsible for problem solving, emotion, and complex thought.

MOTOR VEHICLE CRASHES AND OTHER INJURIES

Motor Vehicle Crashes

Sleepiness is a significant, and possibly growing, contributor to serious motor vehicle injuries. Almost 20 percent of all serious car crash injuries in the general population are associated with driver sleepiness, independent of alcohol effects (Connor et al., 2002). Driver sleepiness is most frequently a manifestation of sleep loss, as discussed below, but other sleep disorders, which have lower prevalence, contribute to the problem, including sleep-disordered breathing, restless legs syndrome, and narcolepsy.

The 20 percent figure, cited above, is the population-attributable risk, which is a key public health measure indicating what percentage of car crash injuries, including fatal injuries of passengers, could be avoided by eliminating driver sleepiness. The finding was based on a population-based case-control study in a region of New Zealand in which 571 car drivers and a matched control sample were asked detailed questions about measures of acute sleepiness while driving (Connor et al., 2002). The study adjusted for potential confounding factors, including alcohol. Crashes examined in this study involved a hospitalization or death. The greatest risk factor for the crashes was sleep loss and time of day (driving between 2:00 a.m. to 5:00 a.m.), but sleep apnea symptoms were not risk factors.

Indications are that the public health burden of sleepiness-related injuries is likely increasing, given recent trends in drowsy driving. The National Sleep Foundation found that self-reported drowsy driving has increased significantly over the past years, from 51 percent of respondents in 2001 to 60 percent in 2005 (NSF, 2005). Similarly striking was that more than 10 percent of the entire sample reported nodding off or falling asleep while driving at least 1 to 2 days per month.

The impact of driver sleepiness is similar in magnitude to that of alcohol consumption. A study of all crashes between 1990 to 1992 reported to North Carolina's uniform reporting system found that fall-asleep crashes (ones in which a law officer determines the driver to be asleep or fatigued) and alcohol-related crashes were similar in terms of serious injuries (13.5 and 17.8 percent of crashes from all causes, respectively) and fatalities (1.4 and 2.1 percent of all fatalities, respectively) (Pack et al., 1995). In actual driving performance on a closed course, sleep-deprived adults performed as poorly as did alcohol-challenged adults (Powell et al., 2001). After a night of total sleep deprivation, impairments in lane-keeping ability were similar to those found with blood alcohol content of 0.07 percent (Fairclough and Graham, 1999).

Fall-asleep crashes have distinct patterns by type, age, and time of day. According to the North Carolina study, fall-asleep crashes are largely off-the-road and at higher speeds (in excess of 50 mph) (Pack et al., 1995). Adolescents and young adults between the ages of 16 and 29 are the most likely to be involved in crashes caused by the driver falling asleep (Horne and Reyner, 1995; Pack et al., 1995). They account for about 50 percent of all crashes (Horne and Reyner, 1995; Pack et al., 1995). Fall-asleep crashes occur at two periods of day that coincide with circadian variation in sleepiness, in the early morning (2:00 a.m. to 8:00 a.m.) (Pack et al., 1995; Connor et al., 2002) and during the midafternoon (Horne and Reyner, 1995; Pack et al., 1995; Carskadon, 2004). The most common reasons behind fall-asleep crashes are working multiple jobs, night shift work, and sleep duration of less than 5 hours (Connor et al., 2002; Stutts et al., 2003).

Sleep apnea accounts for a small, but measurable percentage of motor vehicle crashes, primarily in drivers above the age of 25 (Sassani et al., 2004). Individuals with sleep apnea are at twice the risk of having a traffic accident as unaffected individuals (Teran-Santos et al., 1999)—the higher the apnea-hypopnea index, the higher the risk (Young et al., 1997a). Sleepy drivers tend to display reduced vigilance, slow reaction times, and loss of steering control. Steering impairment in OSA, sleep deprivation, and alcohol intoxication was compared in a controlled clinical trial. Untreated OSA and sleep deprivation were similar in producing progressive steering deterioration throughout the drive, whereas alcohol-impaired individuals steered equally throughout the drive (Hack et al., 2001). Occupational groups at

high risk of sleep-related crashes are night shift workers (Horne and Reyner, 1995; Ohayon et al., 2002; Drake et al., 2004), medical residents and house staff (Marcus and Loughlin, 1996; Barger et al., 2005), and commercial truck drivers (Walsh et al., 2005).

Commercial truck drivers have attracted the most study because of the prevalence, severity, and public health impact of crashes involving commercial trucks. There are an estimated 110,000 injuries and 5,000 fatalities each year in motor vehicle accidents involving commercial trucks (CNTS, 1996). The National Transportation Safety Board (NTSB) determined that fatigue (including sleepiness) was the probable cause of 57 percent of crashes leading to a truck driver's death (NTSB, 1990a,b). Although this figure is not universally accepted, the definition of *fatigue* by the NTSB is equivalent to the term *sleepiness* or *sleep-related fatigue* used by sleep experts (i.e., fatigue that results in human performance failure) (Walsh et al., 2005). For each truck driver fatality, another three to four people are killed (NHTSA, 1994).

A congressionally mandated study of 80 long-haul truck drivers in the United States and Canada found that drivers had short sleep duration, averaging 5.2 hours in bed and 4.8 hours of sleep per day (Federal Motor Carrier Safety Administration, 1996). Sleep duration was verified electrophysiologically over the 5-day study. Further, commercial drivers have a high prevalence of sleep apnea (Stoohs et al., 1995). Recent studies have found that sleep apnea affects 8 to 15 percent of commercial drivers in the United States and Australia (Gurubhagavatula et al., 2004; Howard et al., 2004).

Work-Related Injuries

Sleep-related fatigue is an independent risk factor in work-related injuries and fatalities, according to two large and well-designed studies (Akerstedt et al., 2002; Swaen et al., 2003). Swaen and coworkers prospectively studied a cohort of more than 7,000 workers in numerous industries in the Netherlands over a 1-year period before studying the occurrence of occupational accidents. During the year they collected information about sleep patterns and other potential risk factors for work-related injuries. The 108 employees who reported being injured during the next year could be assessed for risk factors without recall bias affecting the results. The study found a dose-response relationship between two sleep-related fatigue measures and injuries. For example, highly fatigued workers were 70 percent more likely to be involved in accidents than were workers reporting low fatigue levels, after adjustment for other risk factors. Workers with chronic insomnia were also far more likely than those who were good sleepers to report industrial accidents or injuries (Leger et al., 2002). Finally, disturbed

sleep plays a role in occupational fatalities. In a large 20-year prospective study in Sweden of nearly 50,000 individuals, those reporting disturbed sleep were nearly twice as likely to die in a work-related accident (OR = 1.89, 95% CI 1.22–2.94) (Akerstedt et al., 2002). Similarly, workers who report snoring and excessive daytime sleepiness, indications of sleep apnea, are twice as likely to be involved in workplace accidents, as verified by registry data and after adjusting for all potential confounders (Lindberg et al., 2001).

Falls in Older People

Falls are a common and costly problem in older people (65 years and older), whether in the community or in long-term care facilities. Each year, more than 30 percent of older people fall (Hausdorff et al., 2001). Falls are the leading cause of death for this particular age group (Murphy, 2000). Although most falls are not directly fatal, they are a leading cause of injuries and trauma-related hospital admissions (Alexander et al., 1992).

Insomnia increases the risk of falling (Brassington et al., 2000). One of the major questions raised by this finding is what is responsible for the increased risk of falls—the underlying insomnia or the use of medication to treat it? Until recently, most of the studies addressing this question were not large enough to yield an answer. In 2005, a large, prospective study of 34,000 nursing home residents across the state of Michigan ruled out use of hypnotic medications as a risk factor for falls (Avidan et al., 2005). In fact, the study found that treated insomnia, and untreated insomnia, but not hypnotic medications, were predictors of falls. Although the results of this study did not find that insomnia increased the risk of hip fractures, other studies have found an association (Fitzpatrick et al., 2001). Preliminary data from the Study of Osteoporosis in Women also indicate an increased risk of falls associated with decreased sleep efficiency and sleep time (as measured objectively using actigraphy) in a large group of older women, with effects persisting after adjustment of health status and mood and other confounders (Stone et al., 2004).

Interventions

There have been a few studies that have examined the effect of interventions on improving the outcomes associated with sleepiness. A range of regulatory, technological, and therapeutic approaches are possible to ameliorate the problem of sleepiness among commercial drivers (Walsh et al., 2005). However, there has been limited study of the benefit of these strategies. Thus, before additional rules and regulations are developed, analysis of the effec-

tiveness of the current regulations and statutory items is needed. This analysis will help the establishment of much-needed future rules and regulations pertaining to sleep loss and fatigue. Preplanned naps have been successfully tested in crew members on transmeridian flights; the findings show that safe and feasible rotations occurred as crew members took brief, 40-minute nap periods, and the naps improved alertness (Graeber et al., 1986a,b). Similarly, a study of Italian policemen who patrol highways found that prophylactic naps before a night shift can lower the risk of motor vehicle accidents during the shift, according to a combination of retrospective questionnaire, prospective analysis, and mathematical modeling (Garbarino et al., 2004)

The strongest evidence for the public health benefits of treatment comes from clinical trials and retrospective studies of the impact of CPAP therapy for sleep apnea. These studies also dispel any doubt of the causal relationship between sleep disorders and accidents. In a randomized, controlled clinical trial, 59 men with sleep apnea were assigned either to therapeutic CPAP or subtherapeutic CPAP. The latter does not deliver enough pressure to open the pharynx and achieve a therapeutic effect. One month later the men were placed in a steering simulator. Therapeutic CPAP significantly improved their steering performance and reaction time relative to subtherapeutic CPAP (Hack et al., 2000). Previous clinical trials had also shown CPAP to be effective in terms of reducing the rate of self-reported automobile crashes and performance on driving tests, but they were uncontrolled (Cassel et al., 1996; Krieger et al., 1997). A review and meta-analysis estimates that nearly 1,000 lives would be saved annually if all drivers with OSA were treated with CPAP (Sassani et al., 2004).

IMPACT ON FUNCTIONING AND QUALITY OF LIFE

Sleep problems, difficulty initiating and maintaining sleep, nonrestorative sleep, and excessive daytime sleepiness are associated with adverse effects on well-being, functioning, and quality of life, according to numerous studies covering the general population (Baldwin et al., 2001, 2004; Hasler et al., 2005; Strine and Chapman, 2005), working people (Kuppermann et al., 1995), and clinical populations (Simon and VonKorff, 1997), including pediatric samples (Rosen et al., 2002). Studies have used various measures of quality of life and functional status, the most common of which is a validated questionnaire known as the SF-36, a 36-item measure that asks about eight domains: (1) physical functioning; (2) role limitation due to physical health problems (role physical); (3) bodily pain; (4) general health perceptions; (5) vitality; (6) social functioning; (7) role limitations due to emotional health problems (role emotional); and (8) mental health. A similar measure is the health-related quality of life survey, which asks fewer questions. Individuals who suffer from primarily sleep apnea, narcolepsy,

restless legs, primary parasomnias, and insomnia constantly report poorer quality of life compared to population norms (Reimer and Flemons, 2003).

Using health-related measures of quality of life, the functional impact of sleep loss was assessed by a large and nationally representative survey, the United States Behavioral Risk Factor Surveillance System (Strine and Chapman, 2005). The study focused on nocturnal sleep time in nearly 80,000 respondents. About 26 percent of the respondents reported obtaining insufficient sleep on a frequent basis (not enough sleep on 14 days or more over the past 30 days). This group was significantly more likely than those without frequent sleep insufficiency to report poorer functioning and quality of life on each of the eight items of the health-related quality of life.

Several studies have dealt with insomnia and its adverse impact on quality of life (Zammit et al., 1999; Leger et al., 2001; Katz and McHorney, 2002). People with severe insomnia reported lower quality of life on all eight domains of the SF-36 (Leger et al., 2001). Their low quality-of-life ratings were similar to ratings by patients with congestive heart failure and depression, according to a study of nearly 3,500 primary care patients (Katz and McHorney, 2002) (Figure 4-3). About 16 percent of the sample had severe insomnia, and the study adjusted for numerous factors including health habits, obesity, other chronic conditions, and severity of disease. A study of a large health maintenance organization population (n = 2,000) found that insomnia (versus no current insomnia) was associated with significantly greater impairment, as measured by the self-rated Social Disability Schedule and the interviewer-rated Brief Disability Questionnaire. Individuals with insomnia also had more days of restricted activity due to illness

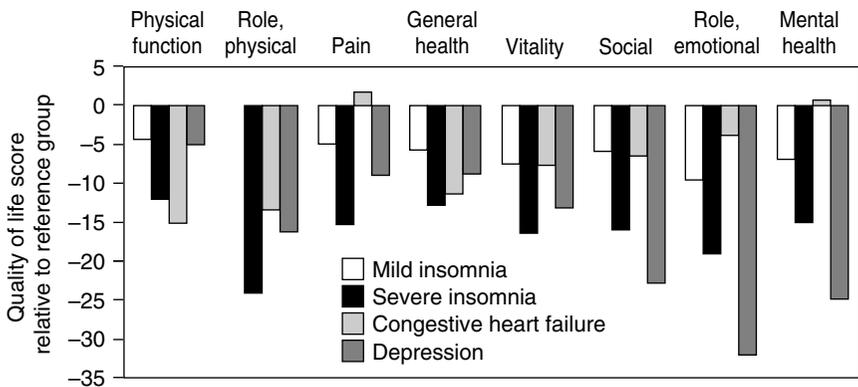


FIGURE 4-3 Severe insomnia affects quality of life.
SOURCE: Edinger and Means (2005).

and more days spent in bed (Simon and VonKorff, 1997). One study revealed a dose-response relationship, with higher levels of insomnia being associated with greater impairments in the ability to accomplish daily tasks and decreased enjoyment of interpersonal relationships (Roth and Ancoli-Israel, 1999).

Individuals with severe OSA also report significantly poorer quality of life, and mild OSA is also associated with reduced vitality (Baldwin et al., 2001). These effects are similar to those of other chronic diseases in the general population in the United States. Individuals with OSA who are compliant with CPAP treatment report improved changes in vitality and quality of life 2 months after the onset of CPAP treatment (Redline et al., 1998).

Symptoms of restless legs syndrome are associated with lower quality of life (Unruh et al., 2004), similar to the quality of life of individuals with type 2 diabetes mellitus and acute heart attack (Allen et al., 2003). Restless legs syndrome also affects marital relationships. Approximately one-third of couples sleep in separate beds due to the discomfort of their partner's repetitive leg movements (Montplaisir et al., 2005).

Approximately a quarter of children and adolescents report difficulty with sleep (Stein et al., 2001; Archbold et al., 2002). However, very few studies have assessed the association between sleep loss and sleep disorders and health-related quality of life in children. Analysis of a widely used parent report measure of children's physical, emotional, and social functional status and well being—the CHQ-PF50—found the quality of life of their children deteriorated with the severity of OSA (Rosen et al., 2002). This is consistent with a negative association between sleep difficulties and health-related quality of life that was observed in a similar analysis of 80 parents of children referred to a pediatric sleep disorders clinic (Hart et al., 2005). Thus, sleep difficulties may broadly affect a child's development through its impact on children's social, emotional, and physical functioning.

Family and Community Function

The consequences of sleep loss and sleep disorders are not restricted to affected individuals; they also disrupt families and communities. Although relatively sparse, the research described in this section points to widespread impact on the health and well-being of sleep partners and/or other family members. Their sleep quality and health can be disrupted, as can their well-being, income, and capacity to care for children or ill family members. Adverse effects on family cohesiveness, in turn, can lead to severe family turmoil and divorce. Similarly, sleep disruption of family caregivers has broader societal effects by contributing to hospitalization or nursing home placement of ill family members for whom they provide care.

Most research on families and communities deals with bed partners of individuals with a sleep problem. Bed partners of individuals with sleep-disordered breathing report a lower quality of life, based on the SF-36 survey than the sleep-disordered breathing patients (Breugelmans et al., 2004). Further, in a large population-based sample of older individuals, bed partners report poor health, depressed mood, poor mental health, and marital unhappiness (Strawbridge et al., 2004).

Does CPAP therapy improve bed partners' sleep? At least four studies have addressed this question, with three showing improvement. Two of the studies that demonstrated a benefit were nonrandomized and used a *before* versus *after* study design. After approximately one month of CPAP therapy, partners experienced less daytime sleepiness as measured by the Epworth Sleepiness Scale and improved quality of life as measured by the SF-36 scale (Doherty et al., 2003; Parish and Lyng, 2003). A small, polysomnographic study of individuals using CPAP found that their partners show fewer arousals and greater sleep efficiency in the hours after CPAP's introduction versus the hours before (Beninati et al., 1999). The improvement in sleep efficiency (percentage of time asleep while in bed) translated to an extra hour of sleep per night. The only placebo-controlled study found that CPAP is associated with subjective improvement in bed partners' sleep (via the Pittsburgh Sleep Quality Inventory), but no objective improvement, as measured by polysomnography (McArdle et al., 2000).

Sleep-disordered breathing has also been found to heighten the rate of divorce and the use of paid personal leave, among other effects, according to a study of obese individuals with OSA. A team of Swedish researchers, studying a large registry of obese subjects, found that individuals with OSA (as defined by symptoms of snoring and daytime sleepiness) report about three times the rate of divorce of those without OSA and/or daytime sleepiness (Grunstein et al., 1995). The effects are even more pronounced among the women in the sample with OSA ($n = 155$). Men with OSA ($n = 338$) reported less income, and both genders reported more sick leave and disturbed work performance. These effects were independent of the effects of obesity and other health factors. In a separate study, 60 percent of bed partners reported that they slept apart versus 20 percent of controls. Although the partners' level of marital satisfaction was similar to controls', the partners reported greater dissatisfaction with the sleep behaviors of their apneic spouses (Billmann and Ware, 2002).

A common complaint of parents is being awakened by a young child with a sleep problem. Sleep loss is indeed reported more frequently by parents after the birth of a child than during pregnancy (Gay et al., 2004). Improvement in parents' sleep quality, as well as improvement of family well-being, occurs after the introduction of a behavioral intervention designed to train parents to overcome sleep problems in young children

through a graduated conditioning program known as extinction (Eckerberg, 2004). Previously, controlled clinical trials had shown that parent training and extinction are effective for treating young children (Mindell, 1999; Ramchandani et al., 2000), but the trials had not measured the impact on sleep and well-being of parents and families.

Sleep disturbances in chronic illness, whether in the affected individual or in the caregiver, affect decisions about hospital or nursing home placement. This is especially true for patients with Alzheimer's disease, considering that up to 44 percent of them have sleep disturbances (Ritchie, 1996; McCurry et al., 1999). Indeed, sleep disturbance in Alzheimer's disease is a common risk factor for nursing home placement (Chenier, 1997; Hope et al., 1998). Sleep hygiene training, targeted at both Alzheimer's disease patients and the caregivers, can improve sleep quality in patients (McCurry et al., 1998, 2003, 2005). One area of future study is whether treating sleep problems (in either the patient or the caregiver) can delay institutionalization. Counseling of caregivers—although not explicitly targeted to their sleep disturbance or that of the patient—has been shown, in a separate randomized trial, to delay nursing home placement (Mittelman et al., 1996). Within nursing homes, behavioral and pharmacological therapies are effective at improving sleep problems (Alessi et al., 1999; Naylor et al., 2000).

ECONOMIC IMPACT OF SLEEP LOSS AND SLEEP DISORDERS

Although problems falling asleep or daytime sleepiness affect 35 to 40 percent of the population (Hossain and Shapiro, 2002), the full economic impact of sleep loss and sleep disorders on individuals and society is not known. There are limited data on the economic impact of insomnia, sleep-disordered breathing, and narcolepsy; the economic impact of other sleep disorders has not been analyzed. As will be discussed in further detail in Chapters 5 and 8, the lack of sufficient data result from inadequate reporting and surveillance mechanisms.

Increased Health Care Utilization

Daytime sleepiness, inadequate sleep time, insomnia, and other sleep disorders place a significant burden on the health care system through increased utilization of the health care system (see below). Patients in the highest quartile of the Epworth Sleepiness Scale are associated with an 11 percent increase in health care utilization, and individuals with sleep-disordered breathing or sleepiness and fatigue are associated with a 10 to 20 percent increase in utilization (Kapur et al., 2002b).

Insomnia

Individuals suffering from insomnia place an increased burden on the health care system (Ohayon and Roth, 2003). Their activity is more limited (Simon and VonKorff, 1997), and they are significantly more likely to access medical and psychiatric care than are individuals that do not have a sleep or psychiatric disorder (Weissman et al., 1997). Individuals with insomnia who also have an associated psychiatric disorder are more likely to seek treatment for emotional problems (14.9 percent versus 8 percent) (Weissman et al., 1997), have a greater number of physician visits, and be admitted to a hospital twice as often (Leger et al., 2002). The burden insomnia place on the health care system is long-term—the majority of individuals with either mild (59 percent) or severe (83 percent) insomnia continue to suffer symptoms of insomnia 2 years after initial diagnosis (Katz and McHorney, 1998). Consequently, individuals suffering from insomnia place a significant economic burden on society resulting in increased health care costs (see below).

Obstructive Sleep Apnea

Individuals with OSA also place a significant burden on the health care system. In the year prior to diagnosis, the medical expenses of individuals with OSA were almost two times as much as control individuals not diagnosed with OSA (\$2,720 vs. \$1,384) (Kapur et al., 1999). Around 80 to 90 percent of OSA cases remain undiagnosed and untreated, which increases the burden of this disorder (Young et al., 1997b; Kapur et al., 2002a). Analysis of health care utilization in Canadians with severe OSA found that during the year prior to diagnosis, individuals with severe OSA spent more than twice the number of days in the hospital compared to controls (251 versus 90). This was associated with an increase in cost of services—\$49,000 to \$99,000 (Kryger et al., 1996). This figure is likely greater in the United States, which also has 10 to 15 percent higher health care utilization associated with severe OSA (Kapur et al., 2002b)—due to higher health care costs compared to Canada. OSA also affects a child's health care utilization. A survey of 287 children with OSA found that in the year prior to diagnosis, children with OSA had a 226 percent increase in health care utilization and had significantly more visits to emergency departments (Reuveni et al., 2002).

A retrospective observational cohort study demonstrated that CPAP treatment reversed the trend of increasing health care utilization observed prior to OSA diagnosis (Bahammam et al., 1999; Albarrak et al., 2005). In a Canadian study, physician visits decreased during the 5 years following CPAP treatment, compared to the 5-year period prior to diagnosis, resulting in lower physician fees (Figure 4-4). After converting to American dol-

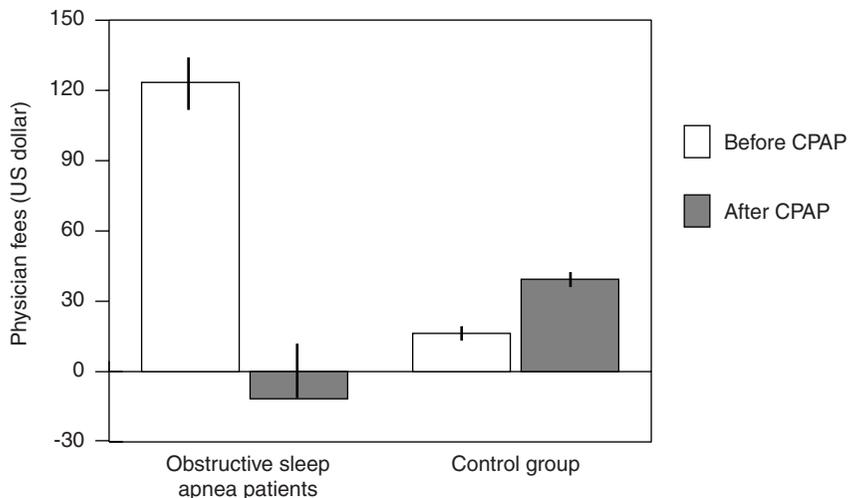


FIGURE 4-4 Effect of CPAP treatment on physician fees.
SOURCE: Albarrak et al. (2005).

lars, mean total fees were greater the year prior to OSA diagnosis ($\$179.09 \pm \32.85) compared to the fifth year after diagnosis ($\$16.77 \pm \33.66) in individuals who were compliant with CPAP treatment (Albarrak et al., 2005). The realized savings would likely be much larger in the United States due to higher associated health care costs.

Direct Costs of Sleep Loss and Sleep Disorders

Billions of dollars are spent each year in the United States on the direct costs of sleep loss and sleep disorders. These medical costs include expenses associated with doctor visits, hospital services, prescriptions and over-the-counter medications. In 1995 the direct cost of insomnia in the United States was estimated to be \$13.9 billion (Walsh and Engelhardt, 1999). Further, based on the costs associated with a laboratory-based polysomnogram, it would cost over \$17.5 billion to test and \$3 billion to treat every person in the United States who has sleep apnea¹ (Sassani et al., 2004). Although it is predicted that the advent of more effective portable monitoring devices (Chapter 6) will decrease the costs associated with testing and diagnosis of sleep disorders, the total direct costs will still remain high and be a burden.

¹Estimates based on a 5 percent prevalence and 2005 estimates of the United States population (295,734,134) and every individual receiving a type 4 polysomnography (CMS code 95810).

Indirect Costs of Sleep Loss and Sleep Disorders

The indirect costs associated with sleep loss and sleep disorders also result in billions of dollars of annual expenditures, including costs associated with illness-related morbidity and mortality, absenteeism, disability, reduction or loss of productivity, industrial and motor vehicle accidents, hospitalization, and increased alcohol consumption (Hossain and Shapiro, 2002). As is the case with direct costs, for each of these categories further analysis is required to determine the complete indirect costs of sleep loss and sleep disorders. The annual economic impact of sleep problems relating to workers inability to adjust to late shifts are estimated to be at minimum over \$60 billion (Table 4-1) (Moore-Ede, 1993). In addition, it has been estimated that sleep-related fatigue costs businesses \$150 billion a year in absenteeism, workplace accidents, and other lost productivity (Sleep Disorders Create Growing Opportunities for Hospitals, 2001).

A 1994 analysis of automobile accidents estimated the cost of accidents attributed to sleepiness to be between \$29.2 to \$37.9 billion (Leger, 1994). Over 50 percent of automobile crashes involving a truck, where a fatality occurred, were caused by sleep-related fatigue, costing approximately \$2.7 million and 4,800 lives (NTSB, 1990a, 1990b; USDOT, 1991; Mitler et al., 2000). However, there is no standardized mechanism to record fatigue- and sleep-related accidents; therefore, these figures are likely underestimates of the total cost of automobile accidents.

Although the complete economic impact of sleep disorders and sleep loss is limited, the available data demonstrates the high burden that inadequate sleep has on the economy. With the average age of the population rising, incidence of sleep disorders is likely to rise, leading to increased costs (Phillips, 2005).

TABLE 4-1 Annual Economic Impact of Sleep Problems Due to Late Shifts

	Cost (billions \$)
Reduced manufacturing productivity	50.0
Increased motor vehicle accidents	5.7
Increased industrial accidents	4.0
Increased accidents, injuries, and deaths at work	2.5
Increase in other medical and psychiatric illnesses	2.0
Personnel turnover and retraining	1.0
Total	65.2

SOURCE: Moore-Ede (1993).

Economic Impact of Insomnia

The total cost estimates of insomnia range from \$30 billion (Walsh and Engelhardt, 1999) to \$107.5 billion (Stoller, 1994). The large variation in the range is attributed to the underlying assumptions about the prevalence of insomnia in the United States, which range from 10 to 33 percent. However, it is evident that even using more conservative prevalence estimates the total annual costs in the United States exceeds tens of billions of dollars.

Direct Cost

In 1995 the direct costs of insomnia totaled approximately \$13.96 billion (Table 4-2). However, this is an underestimate of the total costs, as approximately 12 percent of all physicians, including hospital-based or government employed physicians (including doctors in VA hospitals), were not included in these estimates. In 2002 it was estimated that in the United States 27 million prescriptions were filled for hypnotics, worth about \$1.2 billion (Mendelson, 2005). Calculations based on medical claims showed that increased physician fees and medical expenses for elderly and non-elderly patients with insomnia were respectively \$5,580 and \$4,220 higher

TABLE 4-2 The Direct Costs of Insomnia in the United States for 1995

	Costs (millions \$)
<hr/>	
Substances used for insomnia	
Prescription medications	809.92
Nonprescription medications	325.80
Alcohol	780.39
Melatonin	50.00
Total Cost of Substances	1,966.11
Health care services for insomnia	
Outpatient physician visits	660.00
Psychologist visits	122.40
Social working visits	75.30
Sleep specialist visits	18.20
Mental health organizations	153.00
In-patient hospital care	30.80
Nursing home care	10,900.00
Total	11,960.70
Total direct costs	13,926.11

SOURCE: Walsh and Engelhardt (1999).

than match controls (Ozminkowski et al., 2004), demonstrating the expense incurred by individuals with insomnia.

In 1995 over 78 percent of direct costs associated with insomnia, \$11.96 billion, was spent on nursing home care (Walsh and Engelhardt, 1999), a 132 percent increase since 1990 (Walsh et al., 1995). Although this proportion may seem high, almost half of the population over 65 years of age report difficulty with sleep (Mellinger et al., 1985), and 20.4 percent of admissions to a nursing home were attributed to sleep disturbances (Walsh and Engelhardt, 1999).

Two factors contribute to these higher costs associated with insomnia. First, the general population is typically reluctant to consult doctors about their sleep problems, and second, inadequate physician training prevents proper recognition, diagnosis, and treatment of patients with insomnia (see Chapters 5 and 7) (Walsh and Engelhardt, 1999; Benca, 2005; NIH, 2005).

Indirect Cost

To date there has not been a detailed analysis assessing the total indirect costs associated with insomnia. A 1988 study estimated that productivity loss resulting from insomnia cost \$41.1 billion (Stoller, 1994). Absenteeism cost more than \$57 billion (Walsh, 2004). Therefore, once the costs of industrial and motor vehicle collisions and related morbidities are included, the indirect cost of insomnia could top \$100 billion.

Insomnia places a greater burden on individuals of lower socioeconomic status (Gellis et al., 2005), those who are less educated, and those who are more likely to be unemployed (Bixler et al., 1979; Karacan et al., 1983; Frisoni et al., 1993; Kim et al., 2000; Li et al., 2002). Falls caused by insomnia also contribute to its economic burden. A greater risk for falls was associated with both hypnotic use (29 percent, OR = 1.29) and insomnia (90 percent, OR = 1.90) (Avidan, 2005). Like other sleep disorders, insomnia is more prevalent in the elderly (Mellinger et al., 1985); therefore, as the United States population continues to age it is expected that the cost associated with falls caused by insomnia will also continue to rise.

Economic Impact of Obstructive Sleep Apnea

Direct Cost

Similar to other sleep disorders, there is very limited data on the direct costs associated with obstructive sleep apnea. Most of the analysis has explored the impact of OSA. The average costs of diagnosis and treatment over five years for an individual is over \$4,000 (Table 4-3) (Chervin et al., 1999; Wittmann and Rodenstein, 2004). An analysis of 97 obese individuals with

TABLE 4-3 Cost of Diagnosis and Treatment of OSA

Polysomnogram	\$1,190
CPAP titration	\$1,190
CPAP equipment and setup	\$1,290
Initial office visits	\$210
Annual follow-up	\$330
Total	\$4,210

SOURCE: Chervin et al. (1999).

OSA in Canada found that over a 2-year period they had almost \$30,000 in expenditures from physician claims and utilized \$49,000 to \$99,000 more in services than their control counterparts (Kryger et al., 1996).

Indirect Cost

There is also limited analysis of the total indirect costs associated with OSA. Based on estimates of from the Sleep Heart Health Study, only 10 to 20 percent of individuals with OSA are estimated to have been diagnosed (Kapur et al., 2002a). The annual medical costs resulting from untreated OSA was \$3.4 billion (Kapur et al., 1999).

Automobile collisions attributed to OSA also contribute to the large economic burden of the syndrome. Sassani and colleagues performed a meta-analysis of PubMed from 1980 to 2003 and investigated the relationship between collisions and OSA (2004). This information was then combined with data from the National Safety Council to estimate OSA-related collisions, costs, and fatalities. Based on this analysis, it was estimated that in the year 2000 more than 800,000 drivers were involved in OSA-related motor vehicle collisions (Sassani et al., 2004). These collisions resulted in loss of life to 1,400 individuals and cost \$15.9 billion. The authors calculated that annually it would cost \$3.18 billion to provide CPAP treatment to all drivers who suffer from OSA, saving 980 lives and \$11.1 billion to \$7.9 billion if the cost of CPAP treatment is taken into account. For every dollar spent on CPAP, \$3.49 would be saved in reduced collision costs. This savings does not include the presumed reduction in the number of accidents at work, decreased health care costs, or improved quality of life (Sassani et al., 2004).

Relationship Between Socioeconomic Status, Race, and Obstructive Sleep Apnea

The relationship between socioeconomic status, race, and obstructive sleep apnea is not well understood. There are limited data that suggest that

the prevalence and severity of OSA is higher in African Americans compared to whites (Scharf et al., 2004), especially in adults under 25 years of age (Redline et al., 1994; Rosen et al., 2002). Compared to whites, African Americans with OSA are more likely to have a higher body mass index (Redline et al., 1994) and a lower mean income (Scharf et al., 2004). Analysis performed between Asians and whites found that OSA in Asians was significantly more severe compared to whites (Ong and Clerk, 1998). However, differences in age, gender, body mass index, or neck circumference did not account for these differences.

Economic Impact of Narcolepsy

The impact of narcolepsy on the economy is also not well understood. A review of the PubMed database through May of 2005 found only one relevant report. It examined narcolepsy's effect on 75 individuals in Germany (Dodel et al., 2004). After converting to American dollars the annual total costs to an individual were \$15,410. The average direct costs accounted for 21 percent of the total expenditures (\$3,310 total), \$1,260 for hospital care, and \$1,060 for medications. However, these figures have been extrapolated from a single German cohort and differences in the organization of their respective health care systems have not been taken into account. Therefore, improved surveillance data are needed to determine the actual economic impact of narcolepsy on the American population.

The socioeconomic status of an individual does not affect the prevalence and severity of narcolepsy; however, narcolepsy may worsen an individual's socioeconomic standing. In Germany individuals with narcolepsy have a significantly higher unemployment rate than average, 59 percent compared to the national average of 9 percent (Dodel et al., 2004). Similarly, studies performed in the United Kingdom (Daniels et al., 2001) and the United States (Goswami, 1998) found that 30 to 37 percent of respondents had lost their job due to narcolepsy.

Summary

Although the data are limited, the effect of sleep disorders, chronic sleep loss, and sleepiness on accident rates, performance deficits, and health care utilization on the American economy is significant. The high estimated costs to society of leaving the most prevalent sleep disorders untreated are far more than the costs that would be incurred by delivering adequate treatment. Hundreds of billions of dollars are spent and/or lost annually as a result of poor or limited sleep. However, greater surveillance and analysis are required to estimate the full economic implications of these problems.

REFERENCES

- ACGME (Accreditation Council for Graduate Medical Education). 2003. *Common Program Requirements (Resident Duty Hours)*. [Online]. Available: <http://www.acgme.org/dutyhours/dutyhourscommonpr.pdf> [accessed May 13, 2005].
- Adams N, Strauss M, Schluchter M, Redline S. 2001. Relation of measures of sleep-disordered breathing to neuropsychological functioning. *American Journal of Respiratory and Critical Care Medicine* 163(7):1626–1631.
- Akerstedt T, Fredlund P, Gillberg M, Jansson B. 2002. A prospective study of fatal occupational accidents—relationship to sleeping difficulties and occupational factors. *Journal of Sleep Research* 11(1):69–71.
- Albarrak M, Banno K, Sabbagh AA, Delaive K, Walld R, Manfreda J, Kryger MH. 2005. Utilization of healthcare resources in obstructive sleep apnea syndrome: A 5-year follow-up study in men using CPAP. *Sleep* 28(10):1306–1311.
- Alessi CA, Yoon EJ, Schnelle JF, Al-Samarrai NR, Cruise PA. 1999. A randomized trial of a combined physical activity and environmental intervention in nursing home residents: Do sleep and agitation improve? *Journal of the American Geriatrics Society* 47(7):784–791.
- Alexander BH, Rivara FP, Wolf ME. 1992. The cost and frequency of hospitalization for fall-related injuries in older adults. *American Journal of Public Health* 82(7):1020–1023.
- Ali NJ, Pitson D, Stradling JR. 1996. Sleep-disordered breathing: Effects of adenotonsillectomy on behaviour and psychological functioning. *European Journal of Pediatrics* 155(1):56–62.
- Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J, et al. 2003. Restless legs syndrome: Diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Medicine* 4(2):101–119.
- Archbold KH, Pituch KJ, Panahi P, Chervin RD. 2002. Symptoms of sleep disturbances among children at two general pediatric clinics. *Journal of Pediatrics* 140(1):97–102.
- Avidan AY. 2005. Sleep in the geriatric patient population. *Seminars in Neurology* 25(1):52–63.
- Avidan AY, Fries BE, James ML, Szafara KL, Wright GT, Chervin RD. 2005. Insomnia and hypnotic use, recorded in the minimum data set, as predictors of falls and hip fractures in Michigan nursing homes. *Journal of the American Geriatrics Society* 53(6):955–962.
- Bahammam A, Delaive K, Ronald J, Manfreda J, Roos L, Kryger MH. 1999. Health care utilization in males with obstructive sleep apnea syndrome two years after diagnosis and treatment. *Sleep* 22(6):740–747.
- Baldwin CM, Griffith KA, Nieto FJ, O'Connor GT, Walsleben JA, Redline S. 2001. The association of sleep-disordered breathing and sleep symptoms with quality of life in the Sleep Heart Health Study. *Sleep* 24(1):96–105.
- Baldwin DC Jr, Daugherty SR. 2004. Sleep deprivation and fatigue in residency training: Results of a national survey of first- and second-year residents. *Sleep* 27(2):217–223.
- Barger LK, Cade BE, Ayas NT, Cronin JW, Rosner B, Speizer FE, Czeisler CA, Harvard Work Hours HaS Group. 2005. Extended work shifts and the risk of motor vehicle crashes among interns. *New England Journal of Medicine* 352(2):125–134.
- Bass JL, Corwin M, Gozal D, Moore C, Nishida H, Parker S, Schonwald A, Wilker RE, Stehle S, Kinane TB. 2004. The effect of chronic or intermittent hypoxia on cognition in childhood: A review of the evidence. *Pediatrics* 114(3):805–816.
- Bedard MA, Montplaisir J, Richer F, Rouleau I, Malo J. 1991. Obstructive sleep apnea syndrome: Pathogenesis of neuropsychological deficits. *Journal of Clinical and Experimental Neuropsychology* 13(6):950–964.

- Beebe DW, Gozal D. 2002. Obstructive sleep apnea and the prefrontal cortex: Towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. *Journal of Sleep Research* 11(1):1–16.
- Belenky G, Wesensten NJ, Thorne DR, Thomas ML, Sing HC, Redmond DP, Russo MB, Balkin TJ. 2003. Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: A sleep dose-response study. *Journal of Sleep Research* 12(1):1–12.
- Benca RM. 2005. Diagnosis and treatment of chronic insomnia: A review. *Psychiatry Services* 56(3):332–343.
- Beninati W, Harris CD, Herold DL, Shepard JW Jr. 1999. The effect of snoring and obstructive sleep apnea on the sleep quality of bed partners. *Mayo Clinic Proceedings* 74(10):955–958.
- Billmann SJ, Ware JC. 2002. Marital satisfaction of wives of untreated sleep apneic men. *Sleep Medicine* 3(1):55–59.
- Bixler EO, Kales A, Soldatos CR, Kales JD, Healey S. 1979. Prevalence of sleep disorders in the Los Angeles metropolitan area. *American Journal of Psychiatry* 136(10):1257–1262.
- Blunden S, Lushington K, Kennedy D, Martin J, Dawson D. 2000. Behavior and neurocognitive performance in children aged 5–10 years who snore compared to controls. *Journal of Clinical and Experimental Neuropsychology* 22(5):554–568.
- Brassington GS, King AC, Bliwise DL. 2000. Sleep problems as a risk factor for falls in a sample of community-dwelling adults aged 64–99 years. *Journal of the American Geriatrics Society* 48(10):1234–1240.
- Breugelmans JG, Ford DE, Smith PL, Punjabi NM. 2004. Differences in patient and bed partner-assessed quality of life in sleep-disordered breathing. *American Journal of Respiratory and Critical Care Medicine* 170(5):547–552.
- Carskadon MA. 2004. Sleep deprivation: Health consequences and societal impact. *Medical Clinics of North America* 88(3):767–776.
- Cassel W, Ploch T, Becker C, Dugnus D, Peter JH, von Wichert P. 1996. Risk of traffic accidents in patients with sleep-disordered breathing: Reduction with nasal CPAP. *European Respiratory Journal* 9(12):2606–2611.
- Chenier MC. 1997. Review and analysis of caregiver burden and nursing home placement. *Geriatric Nursing (London)* 18(3):121–126.
- Chervin RD, Dillon JE, Bassetti C, Ganoczy DA, Pituch KJ. 1997. Symptoms of sleep disorders, inattention, and hyperactivity in children. *Sleep* 20(12):1185–1192.
- Chervin RD, Murman DL, Malow BA, Totten V. 1999. Cost-utility of three approaches to the diagnosis of sleep apnea: Polysomnography, home testing, and empirical therapy. *Annals of Internal Medicine* 130(6):496–505.
- Chervin RD, Clarke DF, Huffman JL, Szymanski E, Ruzicka DL, Miller V, Nettles AL, Sowers MR, Giordani BJ. 2003. School performance, race, and other correlates of sleep-disordered breathing in children. *Sleep Medicine* 4(1):21–27.
- CNTS (Center for National Truck Statistics). 1996. *Truck and Bus Accident Factbook—1994*. UMTRI-96-40. Washington, DC: Federal Highway Administration Office of Motor Carriers.
- Connor J, Norton R, Ameratunga S, Robinson E, Civil I, Dunn R, Bailey J, Jackson R. 2002. Driver sleepiness and risk of serious injury to car occupants: Population-based case control study. *British Medical Journal* 324(7346):1125.
- Daniels E, King MA, Smith IE, Shneerson JM. 2001. Health-related quality of life in narcolepsy. *Journal of Sleep Research* 10(1):75–81.
- Dinges DF, Graeber RC, Carskadon MA, Czeisler CA, Dement WC. 1989. Attending to inattention. *Science* 245(4916):342.

- Dinges D, Rogers N, Baynard MD. 2005. Chronic sleep deprivation. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 67–76.
- Dodel R, Peter H, Walbert T, Spottke A, Noelker C, Berger K, Siebert U, Oertel WH, Kesper K, Becker HF, Mayer G. 2004. The socioeconomic impact of narcolepsy. *Sleep* 27(6):1123–1128.
- Doherty LS, Kiely JL, Lawless G, McNicholas WT. 2003. Impact of nasal continuous positive airway pressure therapy on the quality of life of bed partners of patients with obstructive sleep apnea syndrome. *Chest* 124(6):2209–2214.
- Drake CL, Roehrs T, Roth T. 2003. Insomnia causes, consequences, and therapeutics: An overview. *Depression and Anxiety* 18(4):163–176.
- Drake CL, Roehrs T, Richardson G, Walsh JK, Roth T. 2004. Shift work sleep disorder: Prevalence and consequences beyond that of symptomatic day workers. *Sleep* 27(8):1453–1462.
- Durmer JS, Dinges DF. 2005. Neurocognitive consequences of sleep deprivation. *Seminars in Neurology* 25(1):117–129.
- Eastridge BJ, Hamilton EC, O’Keefe GE, Rege RV, Valentine RJ, Jones DJ, Tesfay S, Thal ER. 2003. Effect of sleep deprivation on the performance of simulated laparoscopic surgical skill. *American Journal of Surgery* 186(2):169–174.
- Eckerberg B. 2004. Treatment of sleep problems in families with young children: Effects of treatment on family well-being. *Acta Paediatrica* 93(1):126–134.
- Edinger JD, Means MK. 2005. Overview of insomnia: Definitions, epidemiology, differential diagnosis, and assessment. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 702–713.
- Emancipator JL, Storfer-Isser A, Taylor HG, Rosen CL, Kirchner HL, Johnson NL, Zambito AM, Redline SR. 2006. Variation of cognition and achievement with sleep-disordered breathing in full-term and preterm children. *Archives of Pediatrics and Adolescent Medicine* 160(2):203–210.
- Engleman HM, Kingshott RN, Martin SE, Douglas NJ. 2000. Cognitive function in the sleep apnea/hypopnea syndrome (SAHS). *Sleep* 23(suppl 4):S102–S108.
- Fairclough SH, Graham R. 1999. Impairment of driving performance caused by sleep deprivation or alcohol: A comparative study. *Human Factors* 41(1):118–128.
- Federal Motor Carrier Safety Administration. 1996. *Commercial Motor Vehicle/Driver Fatigue and Alertness Study*. Washington, DC: Office of Research and Technology.
- Fitzpatrick P, Kirke PN, Daly L, Van Rooij I, Dinn E, Burke H, Heneghan J, Bourke G, Masterson J. 2001. Predictors of first hip fracture and mortality post fracture in older women. *Irish Journal of Medical Science* 170(1):49–53.
- Fletcher KE, Davis SQ, Underwood W, Mangrulkar RS, McMahon LF Jr, Saint S. 2004. Systematic review: Effects of resident work hours on patient safety. *Annals of Internal Medicine* 141(11):851–857.
- Fredriksen K, Rhodes J, Reddy R, Way N. 2004. Sleepless in Chicago: Tracking the effects of adolescent sleep loss during the middle school years. *Child Development* 75(1):84–95.
- Friedman BC, Hendeles-Amitai A, Kozminsky E, Leiberman A, Friger M, Tarasiuk A, Tal A. 2003. Adenotonsillectomy improves neurocognitive function in children with obstructive sleep apnea syndrome. *Sleep* 26(8):999–1005.
- Frisoni GB, De Leo D, Rozzini R, Bernardini M, Buono MD, Trabucchi M. 1993. Night sleep symptoms in an elderly population and their relation with age, gender, and education. *Clinical Gerontology* 13(1):51–68.
- Garbarino S, Mascialino B, Penco MA, Squarcia S, De Carli F, Nobili L, Beelke M, Cuomo G, Ferrillo F. 2004. Professional shift-work drivers who adopt prophylactic naps can reduce the risk of car accidents during night work. *Sleep* 27(2):1295–1302.

- Gay CL, Lee KA, Lee SY. 2004. Sleep patterns and fatigue in new mothers and fathers. *Biological Research for Nursing* 5(4):311–318.
- Gellis LA, Lichstein KL, Scarinci IC, Durrence HH, Taylor DJ, Bush AJ, Riedel BW. 2005. Socioeconomic status and insomnia. *Journal of Abnormal Psychology* 114(1):111–118.
- Goswami M. 1998. The influence of clinical symptoms on quality of life in patients with narcolepsy. *Neurology* 50(2 suppl 1):S31–S36.
- Gottlieb DJ, Chase C, Vezina RM, Heeren TC, Corwin MJ, Auerbach SH, Weese-Mayer DE, Lesko SM. 2004. Sleep-disordered breathing symptoms are associated with poorer cognitive function in 5-year-old children. *Journal of Pediatrics* 145(4):458–464.
- Gozal D. 1998. Sleep-disordered breathing and school performance in children. *Pediatrics* 102(3 Pt 1):616–620.
- Graeber RC, Dement WC, Nicholson AN, Sasaki M, Wegmann HM. 1986a. International cooperative study of aircrew layover sleep: Operational summary. *Aviation Space and Environmental Medicine* 57(12 Pt 2):B10–B13.
- Graeber RC, Lauber JK, Connell LJ, Gander PH. 1986b. International aircrew sleep and wakefulness after multiple time zone flights: A cooperative study. *Aviation Space and Environmental Medicine* 57(12 Pt 2):B3–B9.
- Grantcharov TP, Bardram L, Funch-Jensen P, Rosenberg J. 2001. Laparoscopic performance after one night on call in a surgical department: Prospective study. *British Medical Journal* 323(7323):1222–1223.
- Greenberg GD, Watson RK, Deptula D. 1987. Neuropsychological dysfunction in sleep apnea. *Sleep* 10(3):254–262.
- Grunstein RR, Stenlof K, Hedner JA, Sjostrom L. 1995. Impact of self-reported sleep-breathing disturbances on psychosocial performance in the Swedish Obese Subjects (SOS) study. *Sleep* 18(8):635–643.
- Gurubhagavatula I, Maislin G, Nkwuo JE, Pack AI. 2004. Occupational screening for obstructive sleep apnea in commercial drivers. *American Journal of Respiratory and Critical Care Medicine* 170(4):371–376.
- Hack M, Davies RJ, Mullins R, Choi SJ, Ramdassingh-Dow S, Jenkinson C, Stradling JR. 2000. Randomised prospective parallel trial of therapeutic versus subtherapeutic nasal continuous positive airway pressure on simulated steering performance in patients with obstructive sleep apnoea. *Thorax* 55(3):224–231.
- Hack MA, Choi SJ, Vijayapalan P, Davies RJO, Stradling JR. 2001. Comparison of the effects of sleep deprivation, alcohol and obstructive sleep apnoea (OSA) on simulated steering performance. *Respiratory Medicine* 95(7):594–601.
- Hart CN, Palermo TM, Rosen CL. 2005. Health-related quality of life among children presenting to a pediatric sleep disorders clinic. *Behavioral Sleep Medicine* 3(1):4–17.
- Hasler G, Buysse DJ, Gamma A, Ajdacic V, Eich D, Rössler W, Angst J. 2005. Excessive daytime sleepiness in young adults: A 20-year prospective community study. *Journal of Clinical Psychiatry* 66(4):521–529.
- Hausdorff JM, Rios DA, Edelberg HK. 2001. Gait variability and fall risk in community-living older adults: A 1-year prospective study. *Archives of Physical Medicine and Rehabilitation* 82(8):1050–1056.
- Hope T, Keene J, Gedling K, Fairburn CG, Jacoby R. 1998. Predictors of institutionalization for people with dementia living at home with a carer. *International Journal of Geriatric Psychiatry* 13(10):682–690.
- Horne JA, Reyner LA. 1995. Sleep-related vehicle accidents. *British Medicine Journal* 310(6979):565–567.
- Hossain JL, Shapiro CM. 2002. The prevalence, cost implications, and management of sleep disorders: An overview. *Sleep and Breathing* 6(2):85–102.

- Howard ME, Desai AV, Grunstein RR, Hukins C, Armstrong JG, Joffe D, Swann P, Campbell DA, Pierce RJ. 2004. Sleepiness, sleep-disordered breathing, and accident risk factors in commercial vehicle drivers. *American Journal of Respiratory and Critical Care Medicine* 170(9):1014–1021.
- Howell AJ, Jahrig JC, Powell RA. 2004. Sleep quality, sleep propensity and academic performance. *Perceptual and Motor Skills* 99(2):525–535.
- IOM (Institute of Medicine). 2000. *To Err Is Human: Building a Safer Health System*. Washington, DC: National Academy Press.
- Kapur V, Blough DK, Sandblom RE, Hert R, de Maine JB, Sullivan SD, Psaty BM. 1999. The medical cost of undiagnosed sleep apnea. *Sleep* 22(6):749–755.
- Kapur V, Strohl KP, Redline S, Iber C, O'Connor G, Nieto J. 2002a. Underdiagnosis of sleep apnea syndrome in U.S. communities. *Sleep and Breathing* 6(2):49–54.
- Kapur VK, Redline S, Nieto F, Young TB, Newman AB, Henderson JA. 2002b. The relationship between chronically disrupted sleep and healthcare use. *Sleep* 25(3):289–296.
- Karacan I, Thornby J, Williams R. 1983. Sleep disturbance: A community survey. In: Guilleminault C, Lugaresi E, eds. *Sleep/Wake Disorders: Natural History, Epidemiology, and Long-Term Evolution*. New York: Raven Press. Pp. 37–60.
- Katz DA, McHorney CA. 1998. Clinical correlates of insomnia in patients with chronic illness. *Archives of Internal Medicine* 158(10):1099–1107.
- Katz DA, McHorney CA. 2002. The relationship between insomnia and health-related quality of life in patients with chronic illness. *Journal of Family Practice* 51(3):229–235.
- Kennedy JD, Blunden S, Hirte C, Parsons DW, Martin AJ, Crowe E, Williams D, Pamula Y, Lushington K. 2004. Reduced neurocognition in children who snore. *Pediatric Pulmonology* 37(4):330–337.
- Kim HC, Young T, Matthews CG, Weber SM, Woodard AR, Palta M. 1997. Sleep-disordered breathing and neuropsychological deficits: A population-based study. *American Journal of Respiratory and Critical Care Medicine* 156(6):1813–1819.
- Kim K, Uchiyama M, Okawa M, Liu X, Ogihara R. 2000. An epidemiological study of insomnia among the Japanese general population. *Sleep* 23(1):41–47.
- Krieger J, Meslier N, Lebrun T, Levy P, Phillip-Joet F, Saille J-C, Racineux JL. 1997. Accidents in obstructive sleep apnea patients treated with nasal continuous positive airway pressure: A prospective study. *Chest* 112(6):1561–1566.
- Kryger MH, Roos L, Delaive K, Walld R, Horrocks J. 1996. Utilization of health care services in patients with severe obstructive sleep apnea. *Sleep* 19(9 suppl):S111–S116.
- Kuppermann M, Lubeck DP, Mazonson PD, Patrick DL, Stewart AL, Buesching DP, Fifer SK. 1995. Sleep problems and their correlates in a working population. *Journal of General Internal Medicine* 10(1):25–32.
- Landrigan CP, Rothschild JM, Cronin JW, Kaushal R, Burdick E, Katz JT, Lilly CM, Stone PH, Lockley SW, Bates DW, Czeisler CA. 2004. Effect of reducing interns' work hours on serious medical errors in intensive care units. *New England Journal of Medicine* 351(18):1838–1848.
- Leger D. 1994. The cost of sleep-related accidents: A report for the National Commission on Sleep Disorders Research. *Sleep* 17(1):84–93.
- Leger D, Scheuermaier K, Philip P, Paillard M, Guilleminault C. 2001. SF-36: evaluation of quality of life in severe and mild insomniacs compared with good sleepers. *Psychosomatic Medicine* 63(1):49–55.
- Leger D, Guilleminault C, Bader G, Levy E, Paillard M. 2002. Medical and socio-professional impact of insomnia. *Sleep* 25(6):625–629.
- Li RHY, Wing YK, Ho SC, Fong SYY. 2002. Gender differences in insomnia—A study in the Hong Kong Chinese population. *Journal of Psychosomatic Research* 53(1):601–609.

- Lindberg E, Carter N, Gislason T, Janson C. 2001. Role of snoring and daytime sleepiness in occupational accidents. *American Journal of Respiratory and Critical Care Medicine* 164(11):2031–2035.
- Lockley SW, Cronin JW, Evans EE, Cade BE, Lee CJ, Landrigan CP, Rothschild JM, Katz JT, Lilly CM, Stone PH, Aeschbach D, Czeisler CA, Harvard Work Hours HaS Group. 2004. Effect of reducing interns' weekly work hours on sleep and attentional failures. *New England Journal of Medicine* 351(18):1829–1837.
- Marcus CL, Loughlin GM. 1996. Effect of sleep deprivation on driving safety in house staff. *Sleep* 19(10):763–766.
- McArdle N, Grove A, Devereux G, Mackay-Brown L, Mackay T, Douglas NJ. 2000. Split-night versus full-night studies for sleep apnoea/hypopnoea syndrome. *European Respiratory Journal* 15(4):670–675.
- McCurry SM, Logsdon RG, Vitiello MV, Teri L. 1998. Successful behavioral treatment for reported sleep problems in elderly caregivers of dementia patients: A controlled study. *Journals of Gerontology Series B-Psychological Sciences and Social Sciences* 53(2):122–129.
- McCurry SM, Logsdon RG, Teri L, Gibbons LE, Kukull WA, Bowen JD, McCormick WC, Larson EB. 1999. Characteristics of sleep disturbance in community-dwelling Alzheimer's disease patients. *Journal of Geriatric Psychiatry and Neurology* 12(2):53–59.
- McCurry SM, Gibbons LE, Logsdon RG, Vitiello M, Teri L. 2003. Training caregivers to change the sleep hygiene practices of patients with dementia: The NITE-AD project. *Journal of American Geriatrics Society* 51(10):1455–1460.
- McCurry SM, Gibbons LE, Logsdon RG, Vitiello MV, Teri L. 2005. Nighttime insomnia treatment and education for Alzheimer's disease: A randomized, controlled trial. *Journal of American Geriatrics Society* 53(5):793–802.
- Mellinger GD, Balter MB, Uhlenhuth EH. 1985. Insomnia and its treatment: Prevalence and correlates. *Archives of General Psychiatry* 42(3):225–232.
- Mendelson WB. 2005. Hypnotic medications: Mechanisms of action and pharmacologic effects. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 444–451.
- Millman RP, Working Group on Sleepiness in Adolescents/Young Adults, and AAP Committee on Adolescence. 2005. Excessive sleepiness in adolescents and young adults: Causes, consequences, and treatment strategies. *Pediatrics* 115(6):1774–1786.
- Mindell JA. 1999. Empirically supported treatments in pediatric psychology: Bedtime refusal and night wakings in young children. *Journal of Pediatric Psychology* 24(6):465–481.
- Mitler M, Dement WC, Dinges DF. 2000. Sleep medicine, public policy, and public health. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 3rd ed. Philadelphia: Elsevier/Saunders. Pp. 580–588.
- Mittelman MS, Ferris SH, Shulman E, Steinberg G, Levin B. 1996. A family intervention to delay nursing home placement of patients with Alzheimer disease: A randomized controlled trial. *Journal of the American Medical Association* 276(21):1725–1731.
- Montplaisir J, Allen RP, Walters AD, Lerini-Strambi L. 2005. Restless legs syndrome and periodic limb movements during sleep. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 839–852.
- Moore-Ede MC. 1993. *The Twenty-Four-Hour Society: Understanding Human Limits in a World That Never Stops*. Reading, MA: Addison-Wesley.
- Moss TH, Sills DL. 1981. *The Three Mile Island Nuclear Accident: Lessons and Implications*. New York: New York Academy of Sciences.
- Murphy SL. 2000. Deaths: Final data for 1998. *National Vital Statistics Report* 48(11):1–105.

- Naegele B, Thouvard V, Pepin JL, Levy P, Bonnet C, Perret JE, Pellat J, Feuerstein C. 1995. Deficits of cognitive executive functions in patients with sleep apnea syndrome. *Sleep* 18(1):43–52.
- Naylor E, Penev PD, Orbeta L, Janssen I, Ortiz R, Colecchia EF, Keng M, Finkel S, Zee PC. 2000. Daily social and physical activity increases slow-wave sleep and daytime neuropsychological performance in the elderly. *Sleep* 23(1):87–95.
- NCSDS (National Commission on Sleep Disorders Research). 1994. *Wake Up America: A National Sleep Alert. Volume II: Working Group Reports*. 331-355/30683. Washington, DC: Government Printing Office.
- NHTSA (National Highway Traffic Safety Administration). 1994. *Crashes and Fatalities Related to Driver Drowsiness/Fatigue*. Washington, DC: United States Department of Transportation.
- NIH (National Institutes of Health). 2005. NIH State of the Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults Statement: Manifestations and Management of Chronic Insomnia in Adults. *Journal of Clinical Sleep Medicine* 1(4):412–421.
- NSF (National Sleep Foundation). 2005. *2005 Sleep in America Poll*. [Online]. Available: http://www.sleepfoundation.org/_content/hottopics/2005_summary_of_findings.pdf [accessed June 7, 2005].
- NTSB (National Transportation Safety Board). 1990a. *Safety Study: Fatigue, Alcohol, Other Drugs, and Medical Factors in Fatal-to-the-Driver Heavy Truck Crashes (Volume I)*. Washington, DC: National Transportation Safety Board.
- NTSB. 1990b. *Safety Study: Fatigue, Alcohol, Other Drugs, and Medical Factors in Fatal-to-the-Driver Heavy Truck Crashes (Volume II)*. Washington, DC: National Transportation Safety Board.
- NTSB. 1997. *Grounding of the Liberian Passenger Ship Star Princess on Poundstone Rock, Lynn Canal, Alaska June 23, 1995: Marine Accident Report*. Washington, DC: National Transportation Safety Board [Online] Available: <http://www.nts.gov/publicn/1997/MAR9702.pdf> [accessed March 6, 2006].
- O'Brien LM, Holbrook CR, Mervis CB, Klaus CJ, Bruner JL, Raffield TJ, Rutherford J, Mehl RC, Wang M, Tuell A, Hume BC, Gozal D. 2003. Sleep and neurobehavioral characteristics of 5- to 7-year-old children with parentally reported symptoms of attention-deficit/hyperactivity disorder. *Pediatrics* 111(3):554–563.
- O'Brien LM, Mervis CB, Holbrook CR, Bruner JL, Smith NH, McNally N, McClimment MC, Gozal D. 2004. Neurobehavioral correlates of sleep-disordered breathing in children. *Journal of Sleep Research* 13(2):165–172.
- O'Hara R, Schroder CM, Kraemer HC, Kryla N, Cao C, Miller E, Schatzberg AF, Yesavage JA, Murphy GM Jr. 2005. Nocturnal sleep apnea/hypopnea is associated with lower memory performance in APOE epsilon4 carriers. *Neurology* 65(4):642–644.
- Ohayon MM, Roth T. 2003. Place of chronic insomnia in the course of depressive and anxiety disorders. *Journal of Psychiatric Research* 37(1):9–15.
- Ohayon MM, Lemoine P, Arnaud-Briant V, Dreyfus M. 2002. Prevalence and consequences of sleep disorders in a shift worker population. *Journal of Psychosomatic Research* 53(1):577–583.
- Ong KC, Clerk AA. 1998. Comparison of the severity of sleep-disordered breathing in Asian and Caucasian patients seen at a sleep disorders center. *Respiratory Medicine* 92(6):843–848.
- Ozminkowski R, Wang S, Trautman H, Orsini L. 2004. Estimating the cost burden of insomnia for health plans. *Journal of Managed Care Pharmacy* 10(5):467.
- Pack AI, Pack AM, Rodgman E, Cucchiara A, Dinges DF, Schwab CW. 1995. Characteristics of crashes attributed to the driver having fallen asleep. *Accident Analysis and Prevention* 27(6):769–775.

- Parish JM, Lyng PJ. 2003. Quality of life in bed partners of patients with obstructive sleep apnea or hypopnea after treatment with continuous positive airway pressure. *Chest* 124(3):942-947.
- Phillips B. 2005. *The Future of Sleep Medicine*. Northbrook, IL: American College of Chest Physicians.
- Powell NB, Schechtman KB, Riley RW, Li K, Troell R, Guilleminault C. 2001. The road to danger: The comparative risks of driving while sleepy. *Laryngoscope* 111(5):887-893.
- Ramchandani P, Wiggs L, Webb V, Stores G. 2000. A systematic review of treatments for settling problems and night waking in young children. *British Medical Journal* 320(7229):209-213.
- Randazzo AC, Muehlbach MJ, Schweitzer PK, Walsh JK. 1998. Cognitive function following acute sleep restriction in children ages 10-14. *Sleep* 21(8):861-868.
- Redline S, Kump K, Tishler PV, Browner I, Ferrette V. 1994. Gender differences in sleep-disordered breathing in a community-based sample. *American Journal of Respiratory and Critical Care Medicine* 149(3 Pt 1):722-726.
- Redline S, Strauss ME, Adams N, Winters M, Roebuck T, Spry K, Rosenberg C, Adams K. 1997. Neuropsychological function in mild sleep-disordered breathing. *Sleep* 20(2):160-167.
- Redline S, Adams N, Strauss ME, Roebuck T, Winters M, Rosenberg C. 1998. Improvement of mild sleep-disordered breathing with CPAP compared with conservative therapy. *American Journal of Respiratory and Critical Care Medicine* 157(3 Pt 1):858-865.
- Reimer MA, Flemons WW. 2003. Quality of life in sleep disorders. *Sleep Medicine Review* 7(4):335-349.
- Reuveni H, Simon T, Tal A, Elhayany A, Tarasiuk A. 2002. Health care services utilization in children with obstructive sleep apnea syndrome. *Pediatrics* 110(1 Pt 1):68-72.
- Rhodes SK, Shimoda KC, Waid LR, O'Neil PM, Oexmann MJ, Collop NA, Willi SM. 1995. Neurocognitive deficits in morbidly obese children with obstructive sleep apnea. *Journal of Pediatrics* 127(5):741-744.
- Ritchie K. 1996. Behavioral disturbances of dementia in ambulatory care settings. *International Psychogeriatrics* 8(suppl 3):439-442.
- Roehrs T, Greenwald M, Roth T. 2004. Risk-taking behavior: Effects of ethanol, caffeine, and basal sleepiness. *Sleep* 27(5):887-893.
- Rogers AE, Hwang WT, Scott LD, Aiken LH, Dinges DF. 2004. The working hours of hospital staff nurses and patient safety. *Health Affairs (Millwood)* 23(4):202-212.
- Rosen CL, Palermo TM, Larkin EK, Redline S. 2002. Health-related quality of life and sleep-disordered breathing in children. *Sleep* 25(6):657-666.
- Rosen CL, Storfer-Isser A, Taylor HG, Kirchner HL, Emancipator JL, Redline S. 2004. Increased behavioral morbidity in school-aged children with sleep-disordered breathing. *Pediatrics* 114(6):1640-1648.
- Roth T, Ancoli-Israel S. 1999. Daytime consequences and correlates of insomnia in the United States: Results of the 1991 National Sleep Foundation survey. II. *Sleep* 22(suppl 2):S354-S358.
- Sassani A, Findley LJ, Kryger M, Goldlust E, George C, Davidson TM. 2004. Reducing motor-vehicle collisions, costs, and fatalities by treating obstructive sleep apnea syndrome. *Sleep* 27(3):453-458.
- Scharf SM, Seiden L, DeMore J, Carter-Pokras O. 2004. Racial differences in clinical presentation of patients with sleep-disordered breathing. *Sleep and Breathing* 8(4):173-183.
- Schechter MS. 2002. Technical report: Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics* 109(4):e69.
- Shin C, Kim J, Lee S, Ahn Y, Joo S. 2003. Sleep habits, excessive daytime sleepiness and school performance in high school students. *Psychiatry and Clinical Neurosciences* 57(4):451-453.

- Simon GE, VonKorff M. 1997. Prevalence, burden, and treatment of insomnia in primary care. *American Journal of Psychiatry* 154(10):1417-1423.
- Sleep Disorders Create Growing Opportunities for Hospitals. 2001. *Health Care Strategy Management* 19(2):16-17.
- Spilsbury JC, Storfer-Isser A, Drotar D, Rosen CL, Kirchner LH, Benham H, Redline S. 2004. Sleep behavior in an urban U.S. sample of school-aged children. *Archives of Pediatrics and Adolescent Medicine* 158(10):988-994.
- Stein MA, Mendelsohn J, Obermeyer WH, Amromin J, Benca R. 2001. Sleep and behavior problems in school-aged children. *Pediatrics* 107(4):E60.
- Steinbrook R. 2002. The debate over residents' work hours. *New England Journal of Medicine* 347(16):1296-1302.
- Stoller MK. 1994. Economic effects of insomnia. *Clinical Therapeutics: The International Peer-Reviewed Journal of Drug Therapy* 16(5):873-897.
- Stone KL, Schneider JL, Blackwell T, Ancoli-Israel S, Redline S, Claman D, Cauley JA, Ensrud KE, Hillier TA, Cummings SR. 2004. Impaired sleep increases the risk of falls in older women: A prospective atigraphy study. *Sleep* 27(276 abstract supplement):A125.
- Stoohs RA, Bingham L, Itoi A, Guillemainault C, Dement WC. 1995. Sleep and sleep-disordered breathing in commercial long-haul truck drivers. *Chest* 107(5):1275-1282.
- Stradling JR, Thomas G, Warley AR, Williams P, Freeland A. 1990. Effect of adenotonsillectomy on nocturnal hypoxaemia, sleep disturbance, and symptoms in snoring children. *Lancet* 335(8684):249-253.
- Strawbridge WJ, Shema SJ, Roberts RE. 2004. Impact of spouses' sleep problems on partners. *Sleep* 27(3):527-531.
- Strine TW, Chapman DP. 2005. Associations of frequent sleep insufficiency with health-related quality of life and health behaviors. *Sleep Medicine* 6(1):23-27.
- Stutts JC, Wilkins JW, Scott OJ, Vaughn BV. 2003. Driver risk factors for sleep-related crashes. *Accident Analysis and Prevention* 35(3):321-331.
- Swaen GMH, Van Amelsvoort LGPM, Bultmann U, Kant IJ. 2003. Fatigue as a risk factor for being injured in an occupational accident: Results from the Maastricht Cohort Study. *Occupational and Environmental Medicine* 60(suppl 1):88-92.
- Teran-Santos J, Jimenez-Gomez A, Cordero-Guevara J. 1999. The association between sleep apnea and the risk of traffic accidents. Cooperative group Burgos-Santander. *New England Journal of Medicine* 340(11):847-851.
- Thomas M, Sing H, Belenky G, Holcomb H, Mayberg H, Dannals R, Wagner H, Thorne D, Popp K, Rowland L, Welsh A, Balwinski S, Redmond D. 2000. Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *Journal of Sleep Research* 9(4):335-352.
- Ulfberg J, Carter N, Talback M, Edling C. 1996. Excessive daytime sleepiness at work and subjective work performance in the general population and among heavy snorers and patients with obstructive sleep apnea. *Chest* 110(3):659-663.
- United States Senate Committee on Energy and National Resources. 1986. *The Chernobyl Accident*. Washington, DC: Government Printing Office.
- Unruh ML, Levey AS, D'Ambrosio C, Fink NE, Powe NR, Meyer KB. 2004. Restless legs symptoms among incident dialysis patients: Association with lower quality of life and shorter survival. *American Journal of Kidney Disease* 43(5):900-909.
- Urschitz MS, Wolff J, Sokollik C, Eggebrecht E, Urschitz-Duprat PM, Schlaud M, Poets CF. 2005. Nocturnal arterial oxygen saturation and academic performance in a community sample of children. *Pediatrics* 115(2):204-209.
- USDOT (United States Department of Transportation). 1991. *The Costs of Highway Crashes*. Washington, DC: Federal Highway Administration.

- USNRC (United States Nuclear Regulatory Commission). 1987. *Report on the Accident at the Chernobyl Nuclear Power Station*. NU-REG 1250. Washington, DC: Government Printing Office.
- Van Dongen HP, Maislin G, Mullington JM, Dinges DF. 2003. The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 26(2):117–126.
- Wahlstrom KL, Davison ML, Choi J, Rossm JN. 2001. *Minneapolis Public Schools Start Time Study: Executive Summary—August 2001*. Twin Cities, MN: University of Minnesota.
- Walsh JK. 2004. Clinical and socioeconomic correlates of insomnia. *Journal of Clinical Psychiatry* 65(suppl 8):13–19.
- Walsh JK, Engelhardt CL. 1999. The direct economic costs of insomnia in the United States for 1995. *Sleep* 22(suppl 2):S386–S393.
- Walsh JK, Engelhardt CL, Hartman PG. 1995. The direct economic cost of insomnia. In: Nutt DJ, Mendelson WB, eds. *Hypnotics and Anxiolytics*. London: Bailliere Tindall.
- Walsh JK, Dement WC, Dinges DF. 2005. Sleep medicine, public policy, and public health. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 648–656.
- Weaver TE, George CFP. 2005. Cognition and performance in patients with obstructive sleep apnea. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 4th ed. Philadelphia: Elsevier/Saunders. Pp. 1023–1033.
- Weissbluth M, Liu K. 1983. Sleep patterns, attention span, and infant temperament. *Journal of Developmental and Behavioral Pediatrics* 4(1):34–36.
- Weissman MM, Greenwald S, Nino-Murcia G, Dement WC. 1997. The morbidity of insomnia uncomplicated by psychiatric disorders. *General Hospital Psychiatry* 19(4):245–250.
- Wittmann V, Rodenstein DO. 2004. Health care costs and the sleep apnea syndrome. *Sleep Medicine Reviews* 8(4):269–279.
- Wolfson AR, Carskadon MA. 1998. Sleep schedules and daytime functioning in adolescents. *Child Development* 69(4):875–887.
- Wolfson AR, Carskadon MA. 2003. Understanding adolescents' sleep patterns and school performance: A critical appraisal. *Sleep Medicine Reviews* 7(6):491–506.
- Young T, Blustein J, Finn L, Palta M. 1997a. Sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. *Sleep: Journal of Sleep Research and Sleep Medicine* 20(8):608–613.
- Young T, Evans L, Finn L, Palta M. 1997b. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep* 20(9):705–706.
- Zammit GK, Weiner J, Damato N, Sillup GP, McMillan CA. 1999. Quality of life in people with insomnia. *Sleep* 22 (suppl 2):S379–S385.

5

Improving Awareness, Diagnosis, and Treatment of Sleep Disorders

CHAPTER SUMMARY *The public health burden of chronic sleep loss and sleep disorders coupled with the low awareness among the general population, health care professionals, and policy makers requires a well-coordinated strategy to improve sleep-related health care. Increasing the awareness and improving the diagnosis and treatment of sleep disorders necessitates a multipronged effort that includes three key components: public education, training for health professionals, and surveillance and monitoring. First, a public health campaign is required to increase awareness among the general population. Second, specific education and training strategies are needed to increase awareness among health care professionals, including improved curriculum content and certification requirements. There are a number of surveillance and monitoring tools, but very few examine issues pertaining to sleep loss and sleep disorders. Thus, third, improved surveillance and monitoring of the general population is needed. The preeminent goal of this strategy is to create and sustain a broad societal commitment to engaging in proper sleep habits as a primary tenet of health. Such a commitment will involve participation by those individuals and organizations in a position to educate the public at national, state, local, and community levels—including K–12 education, colleges and universities, medical schools and other health profession education programs, hospitals, community clinics, local health departments, private industry (e.g., transportation, manufacturing facilities, nursing homes), and entertainment media. It will also require simultaneous investment in public education cam-*

paigns for all age groups as well as a sustained effort to integrate sleep-related content into curricula of undergraduate health science programs all the way through continuing education programs for health professionals.

CHALLENGES FACING INDIVIDUALS WITH SLEEP DISORDERS

Sleep is often viewed by the general public as a “perceptual hole in time”—during which nothing productive occurs (Dement and Vaughn, 1999). One only has to examine common colloquialisms such as “don’t get caught napping,” “if you snooze you loose,” or “time is money” to gain a sense of the prevailing attitude that sleep is either optional, a luxury, or unimportant. In fact, being able to “get by on 4 hours of sleep” (and thus being able to increase productivity) is often considered an enviable trait.

Daily sleeping and waking patterns are no longer driven by the light and dark cycle but, rather, by work schedules, economic interests, and increasing globalization. Unfortunately, the resulting “24/7” schedules are typically not optimal in terms of filling physiological requirements for sleep. Thus, daytime sleepiness and its consequences are becoming increasingly common problems affecting up to 15 percent of the population (Punjabi et al., 2003). For some, sleep disruption and constant sleepiness are often deemed an inevitable part of their social roles as spouses, workers, caregivers, and so on. Although improving diet and exercise as a part of a healthy lifestyle program is acceptable, sleep continues to be considered an expendable luxury (Dzaja et al., 2005). Thus, performance and social responsibilities may often take precedence over sleep, largely because of multiple role demands and expectations.

Stigma is a problem that often complicates chronic illness. Acceptable standards for roles and activities are socially determined, and individuals who deviate from these expectations because of chronic illness are often labeled as “different” and are thus stigmatized (Falvo, 2005). Similarly, individuals with certain sleep disorders, which are often chronic in nature, may also be stigmatized because of the inability to fulfill role expectations. An additional factor that may underlie this stigma is that sleep is typically misperceived as an “asocial” activity. However, sleep is actually a very important type of social interaction—an activity that is negotiated with self, family, friends, employers, lawmakers, fellow drivers on the road, and so on (Meadows, 2005). When, where, and how sleep occurs is an extremely important sociocultural matter (Taylor, 1993; Williams, 2002), and there can be considerable negative sociocultural consequences when the sleep behavior, either intentionally or unintentionally, is unacceptable (Mehlman,

2001; Moore et al., 2002). Obesity also presents another challenge to some individuals with sleep disorders. Obesity engenders negative feelings among caregivers, which may affect an individual's health care (Banno and Kryger, 2004).

The lack of awareness among the general public that results from the absence of sleep content in public health education programs causes patients to be hesitant about discussing sleep problems with their health care providers. In addition, fear of being labeled as having a psychiatric problem or exhibiting drug-seeking behaviors are also deterrents (Culpepper, 2002). In the case of insomnia, the most common of all sleep-related complaints, patients typically do not seek help because they believe either that nothing can be done or that the health care providers will do nothing to address the problem (Engstrom et al., 1999).

Patients with excessive daytime sleepiness represent the largest group seeking help at sleep laboratories but often only after they have encountered numerous problems that interfere with performance of normal activities of daily living, their ability to hold a job and maintain a marriage, interact socially, or have had an accident. All too often, these individuals have been labeled lazy or unmotivated. For children with narcolepsy, for example, the stigma associated with their increased daytime sleep tendency can affect social acceptance owing to unusual behavior as well as future risk of increased psychiatric disorders, potential obesity, and depressive symptoms (Dahl et al., 1994; Guilleminault and Pelayo, 1998). Thus, individuals may have to overcome a stigma attached to having a sleep disorder, and seeking appropriate treatment is a very serious issue.

Somnology Public Health Education Campaigns

A review of the National Center on Sleep Disorders Research (NCSDR), Centers for Disease Control and Prevention (CDC), and private foundations demonstrate a limited investment in education and awareness campaigns directed toward increasing the general public's knowledge of the health implications associated with chronic sleep loss and sleep disorders.

National Center on Sleep Disorders Research Public Education Campaigns

The NCSDR was established within the National Heart, Lung, and Blood Institute (NHLBI), partially in response to the previous experience and success the NHLBI had in public education campaigns (see below). As directed by the congressional authorization language, the NCSDR is responsible for coordinating the "disseminat[ion of] public information concerning the impact of sleep disorders and sleep deprivation" (Appendix D)

(U.S. Congress, Senate, 1993). It has also developed a variety of education materials; however, resources have not been devoted to an in-depth evaluation of the effectiveness of these materials. The primary education programs that the NCSDR have initiated include the following:

- *Sleep, Sleep Disorders, and Biological Rhythms* is a curriculum supplement developed for grades 9 through 12 (NHLBI, 2003b). Approximately 12,000 copies of the curriculum supplement have been sent to teachers. There have been more than 11,000 visitors to the sleep curriculum website and 10,000 downloads. More than 2,000 students entered sleep diary data on the Internet.

- The Garfield Star Sleeper Campaign was designed to educate children, parents, educators, and health care providers about the importance of nighttime sleep during childhood (NHLBI, 2005b).

- *Time For Kids* is a magazine on sleep that was developed and distributed by the NCSDR to 30,000 third-grade teachers and the 750,000 children in their classes in connection with National Sleep Awareness Week (NHLBI, 2004).

- The *Healthy Sleep Handbook* is a booklet that will be available to the general public and provide an overview of sleep disorders with signs and symptoms, consequences, and potential treatments. It will explain why sleep is needed, what happens if you don't get enough sleep, and tips on how to obtain enough sleep (NHLBI, 2006).

As these examples demonstrate, apart from campaigns directed toward children and adolescents, which have been inadequately evaluated, the NCSDR has not engaged in widespread multimedia public education campaigns directed toward other susceptible populations, including college students, adults (especially shift workers), elderly people, and high-risk minority populations. This is in part owing to the limited resources of the NCSDR for public education (see Chapter 7). A potential strategy to strengthen these activities is to collaborate with other federal agencies including the CDC, as was directed by the congressional authorization; however, there has been limited involvement of the CDC and other federal agencies in these activities.

Private Foundations Education and Awareness Campaigns

Although limited, private foundations and professional societies, and to a lesser extent patient advocacy organizations, have developed a number of public education programs. A highly successful example is the National Sleep Foundation's (NSF) National Sleep Awareness Week campaign. This campaign coincides annually with the start of daylight savings

time and brings together over 750 sleep centers and 100 government agencies and other nonprofit organizations to plan and implement several public awareness and education projects. Activities have included sleep health fairs, lectures, and a public policy and sleep leadership forum. The NSF also conducts the *Sleep in America* poll, an annual telephone survey that gauges how and when Americans sleep, and created a multimedia educational tool called *Cycles of Sleeping and Waking with the Doze Family* that illustrates information about sleep and includes a website, print materials, and CD-ROM.

Although the Sleep Research Society (SRS) and the American Academy of Sleep Medicine (AASM) are primarily professional societies, they also have contributed to increasing the awareness among researchers, health care providers, and the general public. For example the SRS is a cosponsor of the Trainee Day at annual meeting of Associated Professional Sleep Societies, recently published the Basics of Sleep Research guide, and established the Sleep Research Society Foundation, which annually supports up to six \$20,000 grants. The AASM professional initiatives and public education efforts include among others, the CPAP (continuous positive airway pressure) Compliance Campaign, establishing accreditation programs for sleep technologists and behavioral sleep medicine training programs, and assisting in the development of new clinical practice guidelines. Other private organizations such as the American Sleep Apnea Association, Restless Legs Syndrome Foundation, and Academy of Dental Sleep Medicine have also created smaller public education tools such as patient education brochures, support groups, and online videos.

Educational Activities of the Centers for Disease Control and Prevention

The public education efforts coordinated by the CDC provide additional models that could be used to increase awareness about the health implications of chronic sleep loss and disorders. The CDC has extensive experience in health education and has developed very effective programs in such diverse areas as obesity, colorectal cancer screening, and adolescent health.

The CDC's public information campaign to encourage physical activity includes a website that covers the importance of physical fitness including the health benefits, how much exercise is needed, how to overcome barriers to exercise, and specific tips for becoming more active. The website includes references to documents and other organizations that are resources for individuals interested in this topic (CDC, 2006).

The CDC also partners with other related government and private entities to make these public health campaigns even more effective. For example, the Screen for Life campaign is a successful multimedia colorectal

cancer screening education program in which the CDC has partnered with other organizations including state departments of health, the National Colorectal Cancer Research Alliance, and the Entertainment Industry Foundation. This program targets the general public as well as health professionals and encourages colorectal cancer screening for every person after age 50. In addition to the education and awareness campaign, the CDC also developed a nationwide surveillance program to assess the capacity to perform colorectal cancer screening tests and follow-up for the United States population aged 50 years or older.

One advantage of working with an organization such as the CDC is its credibility and connections to individuals and organizations that can increase program effectiveness. For example, Katie Couric, *NBC Today Show* host, and Academy Award-winning actor Morgan Freeman have served as spokespersons for different campaigns.

Given that chronic sleep loss and sleep disorders are a major public health problem, a public and professional campaign on sleep conditions would fit in well with existing CDC mission and programs.

PUBLIC EDUCATION

Sleep loss and daytime sleepiness affect 30 to 40 percent of the general population (Hossain and Shapiro, 2002); however, millions of individuals suffering from sleep disorders remain undiagnosed and untreated. For example, 80 to 90 percent of obstructive sleep apnea cases remain undiagnosed, which increases the burden of this disorder (Young et al., 1997; Kapur et al., 2002). Most large-scale public health education programs and campaigns to date have focused primarily on diet and exercise and have not included adequate information about sleep. However, the time is right for the development of a sleep campaign. There is a beginning public awareness of the importance of sleep owing to recent articles in the popular press and television programs. Two concurrent strategies are required to increase awareness among the general public: a multimedia public education and awareness campaign, and improved education and training programs to increase awareness among health care professionals.

National Sleep Public Education and Awareness Campaign

Considering the burden that chronic sleep loss and sleep disorders have on all age groups, a multifocal campaign is required to improve awareness among children, adolescents, adults, elderly people, and high-risk populations. The primary role of a campaign would be to improve recognition of the health and economic benefits of proper sleep, as well as educating parents and adults of the consequences associated with not receiving adequate

sleep. In this regard it will be important to inform the public and policy makers of the negative consequences of chronic sleep loss and sleep disorders. The campaign could argue that by taking specific personal actions to improve sleep hygiene, by recommending specific behaviors for all age groups, the adverse health and economic consequences could be reduced.

The need for such a campaign rests on the following assumptions:

- The general public does not recognize the prevalence of, or the consequence associated with chronic sleep loss and/or sleep disorders.
- Most health care providers neither recognize the prevalence of, nor the many risks associated with, chronic sleep loss and/or sleep disorders.
- Many of the technological advances made in the previous century (e.g., television, Internet) serve to deprive people, especially children and adolescents, of needed sleep.
- Sleep loss and sleep disorders are associated with numerous other health complications
- Increased understanding will lead to better sleep behaviors and thus improved health and function.

Treatment of sleep problems, even if only behavioral and educational in nature, has the potential to increase an individual's well-being and productivity. Such a campaign would offer new information to both the general population and health care providers. In addition, the activities of a broad sleep awareness campaign could be linked to all stakeholders—government agencies, private industry, foundations, professional societies, patient advocacy organizations, educators, colleges and universities, and community organizations.

The committee envisions that wherever possible, a national campaign would coordinate activities with local needs and provide for the tailoring of its messages for different communities, including specific age groups, minority groups, and shift workers. In addition, the committee envisions that the campaign should be developed in coordination with the NCSDR, CDC, the proposed National Somnology and Sleep Medicine Research and Clinical Network (see Chapter 8), the Department of Transportation, the Department of Labor, the Department of Education, other relevant federal departments and agencies, with input from private organizations such as the NSF and the AASM. Rigorous evaluation is a critical component. Further, this campaign could be integrated and coordinated with other public health campaigns, including those on obesity and heart disease, with the purpose of increasing the awareness among all Americans of the importance of sleep and the adverse health and social consequences of poor sleep. Further, reinforcing messages should be provided in diverse media and effectively coordinated with other events and dissemination activities.

In proposing the National Sleep Public Education and Awareness Campaign, this committee considered and recognized the associated costs and challenges. These include the following:

- Educating and convincing leaders in the public health field that the health and economic burden associated with chronic sleep loss and sleep disorders requires a national campaign.
- The expenses associated with developing and operating a large nationwide public education and awareness program.
- Coordinating federal, state, and local government agencies that would be involved in a campaign.
- Coordinating the activities of foundations, professional societies, and private companies.
- The large number of individuals experiencing sleep loss or sleep disorders span all age groups, each of which will require a specific strategy.

In summary, although evidence is limited, previously coordinated health education campaigns demonstrate the potential value of efforts designed to increase the awareness of both the prevalence and consequences of chronic sleep loss and sleep disorders. For example, broad coordinated national campaigns such as the NHLBI's National High Blood Pressure Campaign (Roccella, 2002), the National Institute of Child Health and Human Development's (NICHD) Back to Sleep Campaign, the CDC's Screen for Life colorectal cancer campaign, the antitobacco efforts of the late 1960s and early 1970s and the late 1990s and early 2000s (Warner, 1981; Siegel, 2002), and the antidrug campaigns of the middle 1980s (IOM, 2002) have had corresponding reductions in risky behavior.

Back to Sleep Campaign

The Back to Sleep program offers an example of a very successful public education awareness campaign that arose from a strong associative discovery between infant sleeping position and the risk of sudden infant death syndrome (SIDS) (Willinger, 1995; Kemp et al., 1998). In 1993, the American Academy of Pediatrics released its first policy statement on reducing the risk of SIDS that recommended that infants be placed on their backs while sleeping. The following year, the NICHD spearheaded the Back to Sleep campaign. Cosponsors included the Maternal and Child Health Bureau, the American Academy of Pediatrics, the SIDS Alliance, and the Association of SIDS and Infant Mortality Programs. The NCSDR was involved in planning and developing communication materials for the campaign.

Before it was instituted, the death rate for SIDS was approximately 1.3 per 1,000 live births (CDC, 1996). Postsurveillance analysis showed a 50 percent reduction in SIDS rates since the Back to Sleep campaign began (NICHD, 2003). The campaign increased public awareness of SIDS risks and safety through a series of radio and television public service announcements and distribution of more than 20 million pieces of literature to health care professionals and the public.

National High Blood Pressure Education Campaign

Another successful public education program is the National High Blood Pressure Education Program. It was established by the NHLBI in 1972 “to reduce death and disability related to high blood pressure through programs of professional, patient, and public education” (NHLBI, 2005a). The NHLBI coordinates a group of federal agencies, voluntary and professional organizations, state health departments, and numerous community-based programs. At the core of the education activities is the program’s coordinating committee, which follows a consensus-building process to identify major issues of concern and to develop program activities. Each representative from the coordinating committee member organizations work together to provide program guidance and to develop and promote educational activities through their own constituencies. The National High Blood Pressure Education Program is responsible for the five following areas: information collection and dissemination; public, patient, and professional education; community program development; evaluation and data analysis; and technology transfer and electronic distribution of materials.

The education campaign does not depend greatly on advertising, but rather relies heavily on actions by other institutions: campaign organizers working with physicians’ organizations to encourage physicians to provide advice about high blood pressure consistent with national guidelines; proposing stories to newspapers and television and radio that convey the priority messages; and developing affiliations with, and providing materials to, grassroots organizations interested in hypertension (Roccella, 2002). When the program began there was very little awareness and treatment for hypertension. Less than one-fourth of the American population understood the relationship between hypertension and stroke and hypertension and heart disease and only 31 percent sought treatment. Today, more than three-fourths of the population recognizes that relationship and over 53 percent seek treatment (NHLBI, 2005a).

Recommendation 5.1: The National Center on Sleep Disorders Research and the Centers for Disease Control and Prevention should establish a multimedia public education campaign.

The National Center on Sleep Disorders Research—working with the Centers for Disease Control and Prevention, the proposed National Somnology and Sleep Medicine Research Network, private organizations and foundations, entertainment and news media, and private industry—should develop, implement, and evaluate a long-term national multimedia and public awareness campaign directed to targeted segments of the population (e.g., children, their parents, and teachers in preschool and elementary school; adolescents; college students and young adults; middle-aged adults; and elderly people) and specific high-risk populations (e.g., minorities).

To implement this recommendation, the following should be done:

- This campaign should be developed in coordination with appropriate federal departments and agencies and with input from independent experts to focus on building support for policy changes.
- This campaign should be built upon and integrated within existing public health campaigns, including those focused on diet and exercise (e.g., obesity and heart disease).
- Reinforcing messages disseminated through multiple media should be effectively coordinated with events targeting providers of health information such as physicians, nurses, and teachers.

PROFESSIONAL TRAINING AND AWARENESS IS REQUIRED

Societal misperceptions also stem from a lack of professional knowledge about the benefits and impact of sleep. Therefore, the success of the proposed National Sleep Public Education Awareness Campaign particularly relies on increased awareness and more sleep-oriented curricula for the health care providers. Further, underutilization of sleep centers in the United States to assist in diagnosing and treating sleep disorders partly stems from both the lack of public and professional awareness and insufficient training of primary caregivers (Wyatt, 2004). Without widespread recognition of the importance of sleep on the part of both the public and health care providers, society is at significant risk for sleep-related health problems. If health care providers are unaware of the symptoms and problems that occur as a result of compromised sleep, they simply will not pursue the topic with patients. Thus, patient contacts with the health care system are often major sources of “missed opportunities” to diagnose sleep problems and share important information about sleep. In addition, increasing the aware-

ness of health care providers also offers an opportunity to attract health care professionals into the field (see Chapter 7 for detailed discussion). Those who receive sleep-related education are more likely to ask individuals about past or current sleep problems (Haponik and Camp, 1994).

Some progress is being made in developing strategies to improve education and awareness among health care professionals. For example, competency-based goals and teaching strategies for sleep and chronobiology in undergraduate medical education have recently been proposed (Harding and Berner, 2002; Federman, 2003). Similar curricula content has also been developed for undergraduate and graduate nursing programs (Lee et al., 2004). A survey conducted in 1992 revealed that minimal, if any, didactic content on sleep was included in medical and nursing programs (Buysse et al., 2003; Rosen et al., 1998; NHLBI, 2003a). Although curricula in medical and nursing school have been updated since 1992, and there are no recent surveys, anecdotal evidence suggests that sleep-related content is still not adequately addressed. Considerable progress remains to be made.

Treatment of Sleep Disorders Requires Interdisciplinary Training

Sleep disorders vary widely in their complexity, their comorbidities, the risks they represent, and the scope of their manifestations (Chapter 3). They may be a symptom of a behavioral or social change, a secondary manifestation associated with a primary disease, or may be the primary problem. Examination of the disorders associated with each of these categories demonstrates the requirement for educated multidisciplinary health care specialists who have the capacity to recognize, diagnose, and treat chronic sleep loss and sleep disorders. At minimum, there are 13 different health care specialties and subspecialties that are involved in diagnosis and treatment—anesthesiology, cardiology, dentistry, endocrinology, immunology, neurology, nursing, nutrition, otolaryngology, pediatrics, psychiatry, psychology, and pulmonology. For example, individuals with obstructive sleep apnea (OSA) typically require recognition by a primary care physician, and diagnosis and treatment from a sleep specialist who is a pulmonologist, neurologist, psychiatrist, or otolaryngologist. Following, or concurrent with, diagnosis and treatment, the chronic nature of a sleep disorder also may require being seen by a specialist (e.g., endocrinologist for diabetes and obesity, cardiologist for hypertension). Patient and family education, primary care, follow-up and support are often provided by nurses with expertise in the field. Therefore, proper treatment of chronic sleep loss and sleep disorders requires multidisciplinary care. However, as discussed below, there has been very little education of health care professionals about the pathology, etiology, or treatment of chronic sleep loss and sleep disorders.

Undergraduate Sleep-Related Education

Education at the undergraduate level provides a unique opportunity to share important health information when readiness to learn has transcended adolescent levels. It also provides an important opportunity to expose students to the topics and potentially increase the number of individuals interested in this area of medicine. In fact, curricula that include sleep-related material at the undergraduate level may be particularly appropriate and effective for a number of reasons.

First, leaving home to attend college is often the first time that young adults are totally responsible for self-care. Numerous studies have demonstrated that one of the most common difficulties undergrads experience is sleep disturbance. For example, in a survey of 191 college students, most reported that they had developed some form of sleep disturbance (Buboltz et al., 2001). Further, a recent study of 964 undergraduate residence hall students found that sleep problems were among the list of significant predictors of stress (Dusselier et al., 2005). A study of 1,300 students in the United States Military Academy found that incoming cadets were significantly sleep deprived, receiving only about 4 hours and 50 minutes of sleep per night during the week in their first fall semester (Miller and Shattuck, 2005). The reasons for the high prevalence of these sleep problems in undergraduate students are likely related to a variety of factors including poor sleep hygiene, stress associated with changes in lifestyle, study demands, socializing, use of stimulants, and in some cases a feeling of the need to demonstrate mental and physical toughness.

Undergraduates also experience the consequences of poor sleep habits and require the necessary health information to make appropriate lifestyle changes. Earlier studies demonstrated that students' poor sleep quality was associated with increased tension, irritability, depression, confusion, and lower life satisfaction as well as increases use of marijuana and alcohol (Pilcher et al., 1997). In addition, poor sleep has been associated with impaired academic performance and deficits in learning and memory (Lack, 1986; Gais et al., 2000; Stickgold et al., 2000; Walker et al., 2003; Fenn et al., 2003). Unfortunately, many students who experience academic problems do not realize that poor sleep may be a crucial contributing factor (Buboltz et al., 2001).

Chronic Sleep Loss and Sleep Disorders Awareness Programs for Undergraduates

Although some sleep-related public health educational activities have been developed (see previous section), their impact appears to be minimal. Thus, new ways to incorporate sleep education into undergraduate student

life are needed. First and foremost, university administrators need to recognize and acknowledge that students' sleep habits and problems are an important component of campus life. Including content regarding sleep in orientation programs, even in the form of a simple informational flier, may provide a forum for further discussions in other types of programs and activities. Advisors might ask basic questions regarding overall sleep patterns and make recommendations regarding class times that are more compatible with a student's normal sleep patterns. Further, university and college administrators should examine how campus and community environments, such as activities, schedules, sports, and work routines, contribute to sleep disruption (Buboltz et al., 2001) and encourage academic departments to educate their faculty regarding the sleep-related problems of students (Miller and Shattuck, 2005). In addition, awareness campaigns should be developed to target undergraduate students in dormitories and academic health centers. Similar effective programs have been developed for public health campaigns concerning sexually transmitted disease, alcohol abuse, nutrition, and suicide. For example, the American College Athletic Association and the National Association of Student Personnel Administrators have helped design and integrate a number of public health campaigns for college students, such as the Health Education and Leadership Program.

Undergraduate Somnology and Sleep Medicine Curriculum Development

Colleges and universities can both educate students and stimulate interest in the field by making simple cost-effective changes in curriculum. For example, at the United States Military Academy, the general psychology course that is taken by all freshmen now includes information on acute and chronic sleep loss (Miller and Shattuck, 2005). Numerous other types of freshman courses, such as general health, biology, and sports education, might include similar content and easily incorporate it with other health-related information such as nutrition, alcohol and drug abuse, and suicide prevention (Miller and Shattuck, 2005). Offering an elective course, perhaps in collaboration with an academic sleep center, might also help recruit future clinicians and scientists to the field. Curriculum recommendations for both nursing and undergraduate medical students have recently been proposed (Strohl et al., 2003; Lee et al., 2004). Other types of novel activities might include the following:

- Develop undergraduate research experiences in sleep to increase the interactions of these students with graduate students in this area (Box 5-1).
- Develop sleep consortiums among two or more universities and educational programs that could be shared using advanced technology, as the

BOX 5-1

Summer Sleep and Chronobiology Research Apprenticeship

The Summer Sleep and Chronobiology Research Apprenticeship is a unique undergraduate training program in the behavioral sciences at Brown University, which fosters behavioral science research education primarily for undergraduate students, but also for young pre- and post-doctoral scientists. The program provides undergraduate students an intensive research and academic experience in a human sleep and chronobiology research laboratory. It spans 13 weeks, including 2.5 weeks of intensive laboratory skills training, a week attending the annual meeting of the sleep professional societies (APSS), and a 10-week research apprenticeship in an ongoing study of sleep and circadian rhythms in adolescents. The program also supports one or two graduate student teaching assistants, providing role models to the apprentices, additional teaching experience, time for research projects, and full summer stipend. Each year the program concludes with a 2-day "retreat" colloquium. At this retreat, every apprentice is responsible for preparing and presenting a brief talk at the APSS meeting on a research theme they began to examine and researched through the summer.

The National Institute of Mental Health (NIMH) should be commended for funding the training program for 8 years. This brought an unprecedented level of fiscal stability, focus, and opportunity for young trainees. Unfortunately, the NIMH no longer supports undergraduate training programs. The Trans-NIH Sleep Research Coordinating Committee should be encouraged to continue to support similar undergraduate mentorship programs.

Because the program is largely designed for undergraduate students, its success is somewhat difficult to measure. Not every student has gone on to behavioral science research; some are in medicine, others in such disparate fields as law or business. Others, however, have followed the route to graduate study. One former student is working with a noted sleep and chronobiology scientist. Another student is performing research on sleep in birds. A third is a graduate student in neurobiology using electroencephalograms (EEG) and magnetic resonance imaging (MRI) as methods to investigate the relationship between thalamic activation and cortical activation during sleep spindles. Another individual recently received a young investigator award from the European Sleep Research Society (2004, Prague ESRS meeting) for research on adolescent sleep patterns.

numbers of faculty qualified to teach information about sleep may be limited in particular settings.

Students in the clinical health science majors, such as those in nursing and premedicine, should have didactic and associated clinical work in sleep medicine that include specific content in the following:

- Interactions between sleep and health.
- The neurobiology and functions of sleep.
- Effects of restricted or reduced sleep on pathophysiology of diseases.
- Mechanisms that lead to sleep disorders across the life span and across genders.
 - Normal sleep processes across ages, genders, and socioeconomic groups.
 - Effective sleep interventions for sleep disorders (Strohl et al., 2003).

GRADUATE RESEARCH TRAINING IN SOMNOLOGY AND SLEEP DISORDERS

Graduate school is traditionally a time of focused concentration on a specific area of investigation, and the curricular requirements for graduate degrees in biological sciences are typically highly variable among disciplines, programs, and universities. Exposure to research on sleep-related topics is probably most applicable to interdisciplinary programs in neuroscience, as well as to single-discipline programs (e.g., pharmacology, physiology, biochemistry, anatomy, and cell biology). Although the content of these curricula typically depend on the research interests of the local faculty, it is in the interest of the students to have a broad exposure to neuroscience that is usually accomplished via a graduate level survey course in the field, and for that course, or other relevant courses, to include some exposure to sleep-related research. Although there are limited data, it appears that this exposure does not occur. For example, one of the top neuroscience and sleep programs, the neuroscience graduate course in the health sciences and technology program at Harvard University and Massachusetts Institute of Technology, includes only a single lecture on the molecular biology of circadian rhythms and no exposure to sleep-related research (personal communication, C.B. Saper, Harvard University, December 1, 2005).

OVERVIEW OF MEDICAL SCHOOL SOMNOLOGY EDUCATION

The inadequacy of somnology education in medical curricula has been a long-standing issue. As far back as 1978, a survey by the American Sleep Disorders Association (now the AASM) revealed that 46 percent of medical

schools provided no sleep-related education and 38 percent sponsored minimal instruction (Orr et al., 1980). Although the percentage of medical schools that include sleep disorders in their curricula has risen modestly from 54 percent in 1978 (Orr et al., 1980) to 63 percent in 1993, the time devoted averages only 2.11 hours (Rosen et al., 1998). Eighty-nine percent of medical students never performed a clinical evaluation of an individual with a sleep disorder (Rosen et al., 1993).

The situation has slowly improved. A survey performed by a special subcommittee of the AASM, called Taskforce 2000, in 1995 indicated a growth in time devoted to somnology content to 4 hours in the preclinical basic sciences and 2 hours in the clinical clerkships (Rosen et al., 1998). However, structured learning experience in the sleep laboratory and clinical evaluation of individuals with sleep disorder remain limited. Major barriers continue to be lack of time in the medical curriculum, the need for better resources and teaching facilities, and the need for leadership and effective advocacy.

Barriers to Implementation of Sleep-Related Medical Curriculum

Efforts to enhance the training and education in somnology and sleep medicine at all levels of medical education continue to face important challenges. These include the following:

- Somnology and sleep medicine is still a relatively new field, cutting across many traditional disciplinary boundaries. Therefore, there is a need to implement a cohesive, interdisciplinary, and centrally organized sleep medicine curriculum.
 - The importance of sleep to good health is often poorly appreciated; hence, it is underrepresented in the medical curriculum.
 - Somnology and sleep medicine is a budding interdisciplinary field; sleep and circadian rhythms interact and influence nearly every organ system. A coordinated curriculum that includes content related to somnology and sleep disorders is needed in every related teaching block.
 - Limited availability of faculty and mentors with appropriate scientific and clinical expertise creates a need for “content champions” to push the educational agenda in a centrally organized way.
 - A paucity of local educational resources, including clinical infrastructure, exists (Orr et al., 1980; Rosen et al., 1993, 1998; Owens, 2005). As described below, the NIH and AASM have contributed significant resources to the development and establishment of somnology medicine curricula in the past. However, there has been limited evaluation of these efforts.

Sleep Academic Award

From 1996 to 2003 the NCSDR and the NHLBI cosponsored the Sleep Academic Award program. Its primary objective was to develop and evaluate model curricula in somnology and sleep medicine for adaptation into academic institutions. In tandem with curricular development, the Sleep Academic Award program also sought to promote interdisciplinary learning environments and faculty development in somnology and sleep medicine. The model curriculum for medical schools encompassed these four basic core competencies:

- Explain the nature and causation of sleep.
- Discuss the impact of sleep and circadian disorders.
- Perform a sleep history.
- Initiate measures to improve sleep and to reduce sleepiness.

Other Sleep Academic Award professional education initiatives included the addition of sleep questions to board examinations in psychiatry, pediatrics, otolaryngology, and pulmonary medicine; the creation of a sleep clinical case vignette bank for use in objective structured clinical examinations and problem-based learning seminars; the development of continuing medical education lectures and courses; and the implementation of faculty development workshops.

The Sleep Academic Award program also undertook initiatives in graduate medical training related to the effects of sleep loss and fatigue. These initiatives included collaboration with the American Medical Association and the Accreditation Council for Graduate Medical Education (ACGME) on work hours for residents. The MedSleep dissemination initiative distributes educational resources and products for free, including web-based materials, slide sets, videotaped case histories, and curriculum outlines (AASM, 2005). In addition, the AASM Medical Education Committee has established a network of sleep-related education advocates in over 100 of the nation's medical schools to continue the development and implementation of educational materials and to provide evaluation.

Effectiveness of the Sleep Academic Award Program

Although the overall impact and durability of Sleep Academic Award program initiatives have not been measured, they have provided time and money for academic career development in somnology (research and scholarship), training in educational methodology, opportunity for mentorship, and access to leadership positions in professional organizations. Similarly, the durability of institutional impact, while difficult to predict precisely, has

included: provision of teaching, educational support, and materials; increases in the knowledge base of graduates; research opportunities; and engagement of multiple disciplines in somnology and sleep medicine education.

Several empirical studies regarding somnology medical education supported by the Sleep Academic Award program have been published in a special section of the January 2005 edition of *Sleep Medicine*. These studies have shown the following:

- The efficacy of a pediatric screening tool (the BEARS) to increase the amount of sleep information recorded in primary health care settings (Owens and Dalzell, 2005).
- The development and validation of a tool (the Dartmouth Sleep Knowledge and Attitude Survey) in assessing outcomes of educational interventions in sleep medicine (Sateia et al., 2005).
- The impact of education in improving the recognition of sleep disorders in a community-based setting (Zozula et al., 2005).
- The positive impact of lecture and case-based discussion on the performance of medical students in an objective structured clinical examination (Papp and Strohl, 2005).
- The use of the objective structured clinical examination for sleep medicine to gain access to the medical school curriculum by providing objective structured clinical examinations on sleep problems such as obstructive sleep apnea and chronic insomnia (Rosen et al., 2005).

One important outcome of the Sleep Academic Award has been an improvement in the number of somnology and sleep disorders questions on board exams; however, the representation is still low, given the public health burden. For example, the content outline of the board exam for internal medicine indicates zero to two sleep-related questions. The American Board of Otolaryngology lists corrective sleep surgery as 1 of 22 surgical concepts that is covered in the exam, where surgical concepts represents 15 percent of the exam content (American Board of Otolaryngology, 2006). The American Board of Psychiatry and Neurology mentions somnology and sleep disorders as 1 of 20 areas covered in the exam's physiology section—physiology also constitutes 15 percent of the exam (American Board of Psychiatry and Neurology, 2006). The content specifications for the American Board of Pediatrics mentions somnology and sleep disorders 19 times (American Board of Pediatrics, 2006).

Nurses as Care Managers

Another key group of health care providers that could play an especially significant role in advocating healthy sleep and promoting the diag-

nosis and management of sleep problems are nurses—the largest number of health care providers in the United States. Nurses are in a unique position to contribute to new knowledge about sleep and health promotion, provide primary care, as well as monitor sleep habits and disseminate information to patients, and enhance patient compliance with treatment (Lee et al., 2004). Unfortunately, nursing education faces many of the same challenges as other health care provider educational programs regarding the incorporation of sufficient sleep content in its programs. Recently, curriculum recommendations for somnology and chronobiology education for nursing at the undergraduate and graduate level programs have been developed (Lee et al., 2004). These guidelines have been integrated into a limited number of nursing programs; however, greater integration of sleep-related material is required in nursing education programs.

OVERVIEW OF SOMNOLOGY IN MEDICAL RESIDENCY TRAINING CURRICULA

To ensure a high degree of recognition and the most effective clinical care, it is important that more training programs educate residents about the need for early detection and, whenever possible, the prevention of chronic sleep loss and sleep disorders. Primary care providers are largely responsible for this surveillance in the medical system. Therefore, it is imperative that internists, family medicine doctors, and pediatricians are sufficiently trained to assume the surveillance role. As many individuals are referred to pulmonologists, neurologists, psychiatrists, and otolaryngologists for disorders that are related to sleep problems, extensive training in sleep medicine also should be integrated into those program curricula.

The current ACGME program requirements for residency training in internal medicine, family medicine, pediatrics, and psychiatry do not mention chronic sleep loss or sleep disorders. Program requirements for residency in neurology list sleep disorders as one of 22 subjects to be addressed in seminars and conferences. However, except for residency programs in otolaryngology, none of the other four residency program requirements address clinical experiences in sleep medicine (ACGME, 2005a).

Curricula should be designed to ensure that knowledge and skills required to detect the broad range of sleep disorders and to manage those that are not complex should be a component of general competency in each of the five relevant specialty areas of medicine. General competency in somnology and sleep medicine should be certified and recertified by the respective boards of the American Board of Medical Specialties (ABMS). With guidance from the residency review committee of the ACGME, each training program in these five specialty areas must develop curriculum content for somnology and sleep medicine. Departments sponsoring these train-

ing programs have a responsibility to have in place, or alternatively, to identify faculty-level expertise in somnology and sleep medicine, and ensure availability of these individuals for learners in the residency training program. As a result of the multidisciplinary nature of sleep medicine, interdepartmental sharing of expertise for training should be required in many settings. Clinical experience with diagnosis and management of patients with sleep disorders is preferred to didactic experiences. For this reason, the presence of an institutional sleep disorders clinic, laboratory, or center should be a key component of the educational infrastructure. Exposure of residents to the multidisciplinary nature of sleep evaluation and treatment will best prepare them for roles as primary caregivers, particularly for identification, treatment of simple sleep problems, and triage of more complicated patients to appropriate subspecialists.

Residents should become aware of the general health consequences of sleep disorders, such as the relationship between sleep deprivation and obesity, cardiovascular disease, and behavioral disorders. In addition, subspecialists in internal medicine and pediatric prevention, diagnosis, and treatment should be fully familiar with the sleep-related consequences of chronic disease and incorporate this awareness into their practices and subspecialty fellow training. Providing generalists with sleep-related education would enable them to be competent to care for a substantial number of sleep problems and refer individuals to sleep specialists as needed.

In view of the workforce shortage in the field (see Chapter 7) and the small number of both training programs and individuals enrolled in somnology and or sleep medicine training programs (see below), exposure of residents to this area of medicine will enhance awareness of career opportunities in this discipline and improve clinical care. Thus, the goal of embedding somnology and sleep medicine exposure and experiences in core residency training is to prepare a wide range of individuals to participate as frontline caregivers, and also to ensure that somnology and sleep medicine is visible to learners early in their training process and possibly foster their consideration of somnology or sleep medicine as a career focus. Exposure of residents to discovery and translational research related to sleep medicine might also enhance the attractiveness of the field. Therefore, somnology and sleep medicine investigators should participate, wherever possible, in the residency training process.

OVERVIEW OF SLEEP MEDICINE FELLOWSHIP TRAINING

AASM-Accredited Fellowship Training Programs

Until recently fellowship training programs in sleep medicine were rare, with a small number of academic institutions, hospitals, and other facilities

hosting programs that were not standardized. To address this, a formal accreditation program for fellowship training programs in sleep medicine was established by the AASM. The number of fellowships has grown progressively, particularly over the last decade. There are now 53 fellowship training programs (Table 5-1). Reflecting the multidisciplinary roots of sleep medicine, these training programs are housed in various departments within these institutions.

TABLE 5-1 Accredited Programs for Fellowship Training in Somnology and Sleep Medicine

Date Accredited	Name of Institution	Department Affiliation
1980	Stanford University	Psychiatry and Behavioral Sciences
1989	Center for the Study of Sleep and Waking	Psychiatry and Behavioral Sciences
1991	Detroit Veterans Affairs Medicinal Center	Neurology
1991	Henry Ford Hospital	Pulmonary Division
1992	Mount Sinai Sleep Disorders Center	Pulmonary Division
1993	Michael S. Aldrich Sleep Disorders Laboratory	Neurology and Psychiatry
1993	Newark Beth Israel Sleep Disorders Center	Department of Pulmonary Medicine
1993	University of Pittsburgh School of Medicine	Psychiatry and Medicine, Pulmonary Division
1994	Cleveland Clinic Foundation	Neurology
1995	Mayo Sleep Disorders Center	Pulmonary and Critical Care
1996	Rush University Medical Center	Departments of Psychology and Medicine
1997	Wayne State University	Pulmonary Division
1998	University of Kentucky	Internal Medicine
1998	University of Mississippi Medical Center	Psychiatry
1998	Intermountain Sleep Disorders Center	Pulmonary Division
1999	Children's Memorial Hospital	Pediatrics
2000	Brigham and Women's Hospital	Medicine
2000	Duke University Medical Center	Pulmonary, Clinical Neurology, and Clinical Neuropathology

continued

TABLE 5-1 continued

Date Accredited	Name of Institution	Department Affiliation
2001	Sleep Medicine and Circadian Biology Program/ Indiana University School of Medicine	Pulmonary, Allergy, Critical Care, and Occupational Medicine
2001	State University of New York at Buffalo School of Medicine	Medicine
2001	University of Nebraska Medical Center	Pulmonary Critical Care Section of the Department of Internal Medicine
2001	Rush University Medical Center	Department of Psychology
2001	Northwestern University Medical School	Department of Neurology
2001	Worcester Medical Center Campus at St. Vincent Hospital	Department of Neurology
2001	Scott and White Memorial Hospital and Clinic	Department of Pulmonary/Critical Care
2001	Lahey Clinic	Pulmonology
2001	University of Pennsylvania	Pulmonary, Critical Care, and Sleep Section
2001	Case Western Reserve University	Departments of Medicine, Pedit- rics, and Neurology
2002	Southwestern Medical Center	Department of Psychiatry
2002	Seton Hall University School of Graduate Medical Education	
2002	St. Elizabeth's Medical Center	Pulmonary Division, Department of Medicine
2002	Long Island Jewish Medical Center	Department of Medicine
2002	New Mexico Center for Sleep Medicine	
2002	University of Iowa Hospitals and Clinics Sleep Disorder Center	Neurology
2002	Hackensack University Medical Center Institute of Sleep-Wake Disorders	
2002	Dartmouth Hitchcock Medical Center	Department of Psychiatry
2003	Mayo Clinic/Mayo Graduate School of Medicine, Jacksonville	Division of Education Services
2003	Johns Hopkins University Sleep Disorders Center	Pulmonary/Critical Care

TABLE 5-1 continued

Date Accredited	Name of Institution	Department Affiliation
2003	Tulane University Health Science Center	Comprehensive Sleep Medicine Center
2003	Wake Forest University Health Sciences	Department of Psychiatry
2003	Beth Israel Deaconess Medical Center	Department of Neurology
2003	Beth Israel Deaconess Medical Center	Division of Pulmonary, Critical Care, Sleep Medicine
2003	University of Texas Health Science Center, Houston	Division of Pulmonary, Critical Care, Sleep Medicine
2003	Center for Sleep Disorders at Johnson City Medical Center	Pulmonary/Critical Care/Internal Medicine
2003	University of Wisconsin-Madison	Department of Medicine
2003	Clinilabs, Inc. (Sleep Disorders Institute)	
2003	State University of New York at Buffalo	Department of Neurology
2004	St. Mary's Medical Center/Ultimate Health Services	Regional Sleep Center
2004	University of Washington	Medicine and Neurology
2004	Norwalk Hospital Sleep Disorders Center	Department of Medicine
2004	Temple University Health System Sleep Disorders Center	Department of Internal Medicine, Division of Pulmonary and Critical Care
2004	Washington University School of Medicine	Department of Neurology
2004	University of Louisville/Kosair Children's Hospital	Department of Pediatrics

SOURCE: Personal communication, J. Barrett, AASM, December 12, 2005.

With the complex nature of sleep medicine in mind, the guidelines for accreditation allowed programs to design fellowship training in two ways. The first design allowed for the sleep medicine fellowship to be a minimum of 12 months of training in comprehensive sleep medicine that could be done during or after specialty fellowship training. The second design allowed for the sleep medicine fellowship to be of a combined nature, in

which a substantial portion of the sleep medicine training is embedded within the primary specialty training.

The guidelines for accreditation of fellowship training required that programs provide graduates with clinical, technical, and research experience that promotes sound clinical judgment and a high level of knowledge about the diagnosis, treatment, and prevention of sleep disorders. The guidelines emphasized education in specific content areas, including basic neurological sleep mechanisms; chronobiological mechanisms; cardiovascular, pulmonary, endocrine, and gastrointestinal sleep physiology; specific disorders of sleep; and the psychopharmacology of sleep, as well as the operation of polysomnographic equipment, polysomnographic interpretation, and troubleshooting.

Eligibility requirements for an accredited program include at least one year of training preceded by the completion of an accredited residency program, and sponsorship by an institution that meets fellowship training requirements set forth by the ACGME. The director of the program must be a physician who is a diplomate of the American Board of Sleep Medicine (ABSM), and the program has to be associated with a sleep disorders center accredited by the AASM.

Completion of training in an accredited program satisfies requirements for eligibility to sit for the sleep medicine certification examination administered by the ABSM.

ACGME Sleep Medicine Fellowship Training Programs

In 2002, the AASM submitted an application to ACGME for accreditation of fellowship training programs in sleep medicine. ACGME approved the program requirements for sleep medicine fellowship training programs in June 2004. Accreditation of fellowship training programs by the ACGME now provides a framework for the continued expansion of specialized clinical training in sleep medicine and draws greater attention to the necessity of training programs.

The ACGME fellowship requires 1 year of clinical sleep medicine. Trainees can enter the sleep medicine fellowship if they have been trained in one of the following: general internal medicine (3 years of postgraduate training); neurology (4 years of postgraduate training); psychiatry (4 years of postgraduate training); general pediatrics (3 years of postgraduate training); otolaryngology (5 years of postgraduate training).

In June 2004, ACGME convened a Sleep Medicine Working Group to develop requirements for fellowship training in sleep medicine and formalize the accreditation process. The working group created a comprehensive program guideline that included requirements to ensure competence in core areas, including facility and resources for training, faculty, assignment of

rotation and duty, curriculum, program content, and clinical experience (ACGME, 2005b). The first round of program accreditation was effective July 1, 2005, and 25 programs have received accreditation from ACGME for fellowship training.

DEMONSTRATION OF KNOWLEDGE: BOARD CERTIFICATION

ABSM Certification

In response to increasing recognition and awareness of the importance of sleep and sleep disorders, professional certification in sleep medicine has been administered for physicians and practitioners to demonstrate skill and competence.

The American Sleep Disorders Association (now the AASM) in 1978 established an examination committee. That same year, the committee held the inaugural clinical polysomnography examination; 21 candidates passed the exam. Each year the examination committee received an increasing number of applications, which led to discussions regarding the future of certification. In 1989, the AASM voted to create an independent entity, and in 1991 the ABSM was incorporated and assumed all the activities and responsibilities of the former examination committee.

The ABSM is an independent nonprofit organization and has a board of directors that oversees all aspects of exam administration and governance. The ABSM was self-designated and was not recognized by the ABMS.

Until 2005, the ABSM certification examination consisted of two parts. The part I examination consisted of multiple choice questions covering the basic sciences of sleep, clinical sleep medicine, and interpretation of polysomnogram fragments and other material. Part II was computer-based and consisted of a series of clinical cases with partial polysomnograms, Multiple Sleep Latency Tests, and other relevant data, with candidates typing short answers to questions. The ABSM decided to fuse the two parts of the examination in 2005 and offer a single-day, one-part examination that incorporates the format of both former parts.

Eligibility for the examination is dependent on a candidate fulfilling five requirements as well as possessing acceptable experience in the evaluation of sleep disorders patients. These eligibility requirements ensure adequate and proper education and training—either through an accredited fellowship program or through a combination of training and experience—and competency evaluation through certification of a primary board. Professionals from other clinical disciplines, such as doctoral psychologists and nurses who met all criteria, were also eligible to sit for the examination.

Over the past 14 years, the ABSM certification examination has developed a strong reputation in the medical community and experienced tre-

mendous growth in terms of applicants. The number of candidates applying for the certification examination as well as the number of diplomates (Figure 5-1) has increased dramatically each year; however, as will be discussed in detail in Chapter 6, the capacity is still not sufficient to diagnose and treat all individuals with sleep disorders.

Establishment of the ABMS in Sleep Medicine

Despite its growth in reputation and numbers of diplomates, it became evident by the late 1990s that the ABSM as a freestanding board would not be recognized as fully legitimate by organized medicine. Because sleep medicine requires only 1 year of postresidency fellowship training, the ABSM was ineligible to join the ABMS as an independent board.

In 2002, the ABSM met with several specialty societies and professional organizations to discuss the necessity for certification examination in sleep medicine and the best design for such an examination. A consensus plan was developed for the establishment of a new subspecialty examination in sleep medicine to be jointly offered by the American Board of Internal Medicine, the American Board of Psychiatry and Neurology, and the American Board of Pediatrics; the American Board of Otolaryngology joined later as a sponsoring board. Following further successful negotiations, a plan for this examination was submitted to the ABMS in early 2004. In March 2005, the ABMS announced approval of the certification examination in sleep medicine. A specific time frame for the new examination has not been set; it is expected, however, that the first examination cycle will begin in 2007.

There are three pathways that qualify physicians to sit for the new examination: (1) certification by one of the primary sponsoring boards and

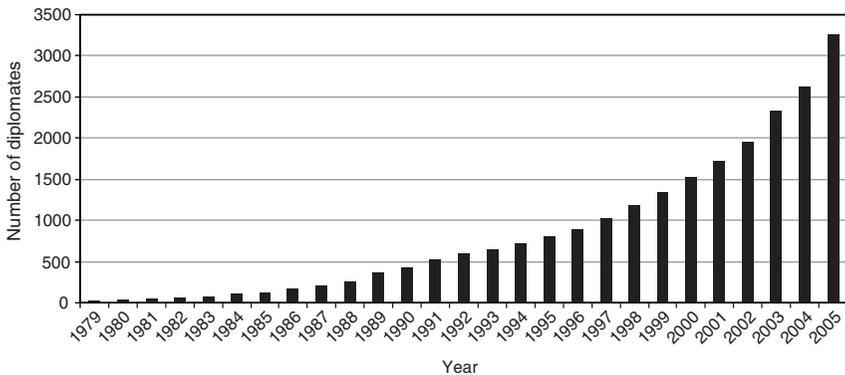


FIGURE 5-1 Total number of diplomates of the ABSM (1979–2005).

SOURCE: Personal communication, J. Barrett, AASM, December 15, 2005.

the current ABSM; (2) certification by one of the primary sponsoring boards and completion of training in a 1-year sleep medicine fellowship program, not overlapping with any other residency or fellowship; and (3) clinical practice experience. This clinical practice experience pathway may consist of a 5-year “grandfathering” period open to physicians who are board certified in one of the sponsoring specialty boards and who can attest that he or she has the equivalent of 1 year of clinical practice experience in sleep medicine during the prior 5 years. This experience could, for example, be gained by an individual practitioner who has devoted one-third of his or her practice to sleep medicine over 3 years. Physicians in the clinical practice pathway will also have to attest to a specified minimum number of patients seen and polysomnograms and Multiple Sleep Latency Tests read. At the end of this initial 5-year period, the only route to board eligibility will be through an ACGME accredited fellowship training program. This creates a one-time, unprecedented opportunity for pulmonologists, neurologists, otolaryngologists, psychiatrists, and other physicians already working in the field to sit for the board examination. However, not all sleep clinicians will be eligible for this accreditation. The ACGME only permits accreditation of doctors, thus nurses, dentists, and doctorally prepared sleep specialists (e.g. psychologists and behavioral health specialists) in other fields are no longer eligible to sit for the examination. As a consequence, there is the potential that in the future particular bodies of knowledge will not be represented in sleep medicine.

Representatives from all four boards are developing and setting standards for the new examination. The American Board of Internal Medicine has administrative responsibility for examination development, and the participating/sponsoring boards have responsibility for setting admission criteria for their own diplomates. These standards and criteria are expected to be announced in 2006.

Although this new structure is based on sleep medicine becoming recognized as an independent specialty, it is too early to tell how well this new approach will work in developing the needed workforce of practitioners for sleep medicine and the next generation of physician-scientists. The fellowship is somewhat unusual in that there is only the requirement for 1 year of training beyond completion of residency. It is unclear whether pulmonologists, who have until now formed the majority of the clinical workforce in sleep medicine (60 percent of diplomates in 2005), will continue to be attracted to the field (Figure 5-2). Clinical requirements for pulmonary medicine involve 18 months of training beyond residency. It appears that this will not count to training in sleep medicine even though there is now a defined curriculum for sleep medicine in pulmonary medicine (American Thoracic Society, 2005) and 10 to 15 percent of the board examination for pulmonary medicine is about sleep disorders. An additional clinical year of train-

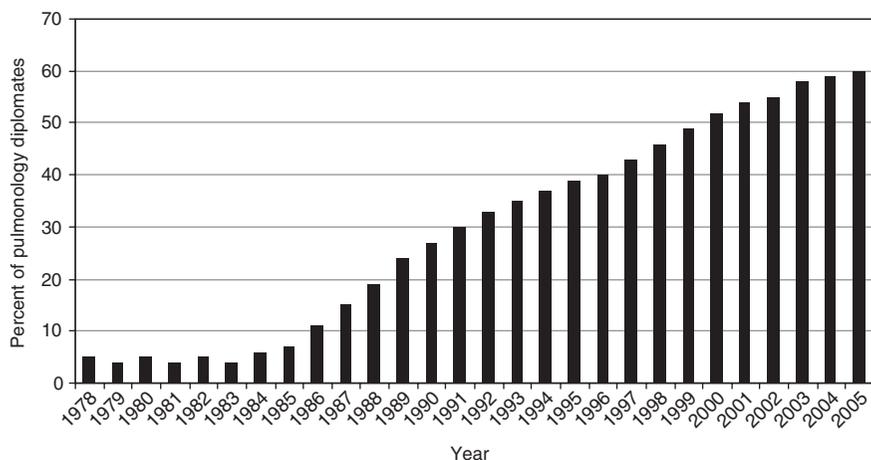


FIGURE 5-2 Percent of pulmonology diplomates of ABSM.

SOURCE: Personal communication, J. Barrett, AASM, December 15, 2006.

ing above and beyond that for pulmonary medicine may represent a barrier to pulmonologists entering this discipline. It is hoped that this issue is addressed, as pulmonologists encompass a significant percentage of the clinical workforce of practitioners in sleep medicine.

Another area of uncertainty is funding for these new sleep fellowships. Previously, when the fellowship was not ACGME-approved, fellows could obtain reimbursements for their clinical activities, including sleep study interpretation. In some other programs, sleep medicine training was incorporated into multiyear research training supported by training grants from the National Institutes of Health (NIH). Neither of these options is available in the new format.

Unfortunately, the rules introduced by the ACGME are not flexible and require 1 complete year of clinical training even in programs that are multi-year and committed to research training. This may have a negative impact on the already fragile pipeline of physician-scientists in this new discipline as outlined elsewhere in this report (see Chapter 7). As described in detail in Chapter 8, the committee encourages the proposed Type II comprehensive academic sleep centers to incorporate research training into their sleep medicine fellowships, while for Type III centers this is considered an essential component.

A final potential limitation of this new examination structure is that it is open exclusively to physicians. Other clinician scientists in fields such as psychology, neuroscience, and nursing will not be eligible to sit for the examination as was the case in prior years. Currently, there are 154 ABSM

PhDs board-certified by the AASM (personal communication, J. Barrett, AASM, January 13, 2006). Excluding these individuals may have an important negative effect on patient access, interdisciplinary nature of sleep programs, and the decision of talented potential scientists and clinicians to pursue the study of somnology.

NEXT STEPS

Medical, nursing, and pharmacy students along with individuals in graduate training, residency, and fellowship training programs require greater exposure to the public health burden of sleep loss and disorders; they also must understand the relationship between sleep problems and the proper diagnosis and treatment of a wide range of medical problems throughout an individual's life span. Although the data are limited, they suggest that focused training about sleep can positively influence the performance of medical students (Haponik and Camp, 1994), residents (Owens and Dalzell, 2005), physicians (Haponik et al., 1996; Rosen et al., 2005; Papp and Strohl, 2005), and primary care clinical staff (Zozula et al., 2005). For example, interns who had previous instruction about sleep-related material often asked patients about past or current sleep problems (82 percent of the time), while sleep histories were rarely obtained by interns who did not have any previous instruction (13 percent of the time) (Haponik et al., 1996).

The challenges that lie ahead, outlined below, are many:

- Sustaining educational initiatives begun by the Sleep Academic Award program.
- Monitoring progress and developing new and updated educational materials, such as sleep objective structured clinical examinations.
- Coordinating efforts across institutions.
- Identifying remaining gaps by assessing the impact of sleep education on physician knowledge, skills, and attitudes; clinical practice; and public health.
- Assessing the relative value and effectiveness of sleep curricula that are integrated across other areas versus those that are stand-alone units.
- Developing means of credentialing nurses, psychologists, and other clinicians who will not qualify for American Board of Medical Specialties certification.
- Integrating sleep-related content into continuing education requirements.

To these ends, educational outcomes research grants and partnerships with appropriate medical subspecialty groups for development and dissemi-

nation of educational programs is essential. Further, many health care-related programs are actively embracing new technologies for teaching (e.g., computer simulations of office practices) that provide an opportunity to ensure that sleep-related materials are incorporated into evolving curricula.

Most important, however, somnology health care providers need to be engaged in curriculum development and implementation. This will enable more effective curricular time and resources necessary for addressing basic educational goals in sleep disorders medicine and for integrating sleep materials into other academic areas. A coordinated curriculum—one that is not departmentally based—offers many advantages to encouraging more rational allocation of time and resources to critical areas of public health, including sleep and its disorders (Reynolds et al., 1995). This could be critical to a new integrative approach to teaching and learning about somnology and sleep disorders for the rest of the medical curriculum.

Recommendation 5.2: Academic health centers should integrate the teaching of somnology and sleep medicine into baccalaureate and doctoral health sciences programs, as well as residency and fellowship training and continuing professional development programs.

The subjects of sleep loss and sleep disorders should be included in the curricula of relevant baccalaureate and graduate educational and research programs of all the health sciences. Similarly, post-graduate, residency, and fellowship training programs, as well as continuing professional development programs, must include this content. The curriculum should expose students in the fields of medicine and allied health fields to the etiology, pathophysiology, diagnosis, treatment, prevention, and public health burden of sleep loss and sleep disorders. Relevant accrediting bodies and licensing boards ought to define sleep-related curriculum requirements and expectations for knowledge and competency (e.g., Liaison Committee on Medical Education, Accreditation Council for Graduate Medical Education, American Board of Medical Specialties, the National League for Nursing, the Commission on Collegiate Nursing Education, and the Council on Education for Public Health). Further, a means for credentialing nonphysicians should be maintained by the American Board of Sleep Medicine, or new mechanisms should be developed by relevant organizations.

DATA SYSTEMS FOR SURVEYING SLEEP AND SLEEP DISORDERS

Adequate public health education not only requires informing public and health care practitioners, but also adequate monitoring of the public health burden. The development of adequate surveillance and monitoring systems is important for informing policy makers, health care providers, researchers, and the public about the effectiveness of health care services, programs, and policies. However, there is currently very little ongoing nationwide surveillance. A number of existing national and state-wide databases that can be used for surveillance and monitoring of disease burden in the United States population are available. The CDC manages and coordinates many of the large national surveys. Two of these databases, the National Health and Nutrition Examination Survey (NHANES) and the National Health Interview Survey (NHIS), have readily available information relevant to chronic sleep patterns and sleep disorders. Other data systems would need to add new components that incorporate sleep-related measures to be of use to researchers in the field. However, not only is it important for new criteria to be added to surveillance and monitoring systems, but researchers must also be encouraged to make use of these datasets.

National Center for Health Statistics

The National Center for Health Statistics (NCHS) is one of the centers of the CDC, and its primary goal is to monitor health trends throughout the nation and to guide actions and policies to improve the health of Americans. The NCHS has permanent surveillance systems of health and disease outcomes (e.g., vital statistics); it also conducts permanently ongoing nationwide studies and surveys. In addition, it conducts special studies as need arises (e.g., supplemental components to national surveys on a limited time basis). As described below, data relevant to sleep research are currently available from some of these systems, but the possibility of additional data collection to fill current knowledge gaps should be carefully considered.

There are a number of major health statistics sources in the United States, stratified according to the local, state, and national nature of their frame. Some sources are purely national (e.g., NHANES, the National Health Care Survey, and the Medical Expenditure Panel Survey); others are state (e.g., Behavioral Risk Factor Surveillance System, the State and Local Area Integrated Telephone Survey) or local (e.g., the National Immunization Survey); yet, the frame for other sources span across all levels of government (e.g., vital statistics, Medicare, and Medicaid).

National Health and Nutrition Examination Survey (NHANES)

Since 1959, a series of health examination surveys of the United States population have been conducted by the CDC and the NCHS. NHANES protocol is designed to monitor the health and nutritional status of Americans. In 1999 NHANES was changed from a periodic survey to an annual survey with public data files released in 2-year periods to protect confidentiality and increase statistical reliability. As in previous national health examination surveys, participants are interviewed in their homes followed by a complete health examination, part of which includes biological specimen collection. The examinations are conducted in a mobile examination center. Each mobile examination center consists of four interconnected specially designed trailers, which house biomedical equipment and laboratory capabilities. An examination team composed of 16 specially trained health professionals and support staff, including a licensed dentist, physician, interviewers, health technicians, and an x-ray technician, operates each mobile examination center.

NHANES monitors the prevalence of diseases and risk factors, nutritional habits and anthropometry status, growth and development, and environmental exposures. Because of its cyclical nature, in addition to its core components, NHANES temporarily adds components (either additional questionnaires or exam procedures). Starting in 2005, and scheduled to end in 2008, a sleep section was added to the household questionnaire. This was done with cosponsorship from the NHLBI and targeted participants in the survey older than 16 years. The NHANES sleep questionnaire is based on instruments previously used in epidemiological studies and includes questions on sleep habits as well as questions on functional outcomes of sleep disorders (Table 5-2).

National Health Interview Survey

The NHIS is the core survey of the Department of Health and Human Services, and since its establishment in 1957 it has been the principal source of information on the health of the civilian noninstitutionalized population of the United States (excluding patients in long-term care facilities, Armed Forces personnel on active duty, and U.S. nationals living abroad). Its main objective is to monitor the health of the U.S. population through the collection and analysis of data on a broad range of health topics. It is designed as a cross-sectional household interview continuously running throughout each year. The current sampling plan was redesigned in 1995, and it is based on a multistage area probability sample that permits the selection of a nationwide representative sample of households on a weekly basis. Approximately 43,000 households (including about 106,000 persons) are successfully re-

TABLE 5-2 NHANES Sleep Questionnaire, 2005–2008

How often do you experience:

- Trouble falling asleep
- Wake up during night/difficulty getting back to sleep
- Wake up too early/difficulty getting back to sleep
- Feel unrested during the day
- Feel excessively sleepy during the day
- Do not get enough sleep
- Take sleeping pills
- Nasal stuffiness, etc., at night
- Leg cramps and leg jerks

Have you ever been told you have a sleep disorder?

- What sleep disorder?
- Sleep apnea?
- Insomnia?
- Restless legs syndrome?

Have you ever snored?

How long does it take for you to fall asleep?

Do you have difficulty carrying out following activities because you are too tired or sleepy:

- Concentrating
- Remembering
- Working on a hobby
- Performing employed or volunteer work
- Operating a motor vehicle

cruited each year. Since 1995, both African American and Hispanic persons are oversampled, and samples are drawn for each state.

The core content of the survey questionnaire (the “basic module”) remains largely unchanged from year to year, thus allowing for trend analyses and for data from more than 1 year to be pooled to increase sample size for analytical purposes. However, survey content is updated every 10 to 15 years. The latest significant revision was put in place in 1997. It includes the Family Core, the Sample Adult Core, and the Sample Child Core. The Family Core includes information on household composition, sociodemographic characteristics, information for matches to administrative databases, and basic indicators of health status and utilization of health care services; it is the sampling frame for additional integrated surveys such as the Medical Expenditure Panel Survey (see below). From each family, one sample adult and one sample child (if any) are randomly selected and given the corresponding core interviews that cover the individual’s health status, disability, health behaviors, use of health care services, and immunizations. In addition to the Basic Module, the NHIS includes a Periodic Module and a Topical Module that contain supplemental sections to respond to new public health data needs as they arise.

The NHIS has only one question related to sleep: “On average how many hours of sleep do you get a night (24-hour period)?”. This question was included in the supplemental surveys administered in 1977, 1985, and 1990, and was added to the core survey in 2004. Based on these data, the percentage of adults who reported sleeping 6 hours or less jumped from approximately 20 percent of the population in 1985 (Schoenborn, 1986) to 25 percent in 2004 (National Center for Health Statistics, National Health Interview Survey, 2004) across all age groups.

One important feature of the NHIS is its use as a sampling frame for other national surveys such as the National Survey of Family Growth and the Medical Expenditure Panel Survey. Because of its relevance for this report, the latter is described in more detail below.

Vital Statistics and the National Death Index

Vital statistics include data on all births and deaths. The latter are based on information contained in the death certificate and include identifying information (name and social security number), demographic data, and data on underlying and contributing causes of death. NCHS’s National Death Index is a resource available to investigators seeking information surrounding the death of individual participants in prospective cohort studies. This is useful for investigators exploring the association between sleep disorders identified in study participants and risk of mortality from certain causes (e.g., cardiovascular, disease, hypertension, depressive disorders, and injuries). It also provides the opportunity to conduct aggregate analyses of distribution and trends of mortality directly attributable to sleep problems.

National Health Care Survey

The National Health Care Survey is a collection of health care provider surveys that obtains information about the facilities that supply health care, the services rendered, and the characteristics of the patients served (Table 5-3). Each survey is based on a multistage sampling design that includes health care facilities or providers and patient records. Data are collected directly from the establishments and/or their records, rather than from the patients. The participating surveys identify health care events—such as hospitalizations, surgeries, and long-term stays—and offer the most accurate and detailed data on diagnosis and treatment, as well as on the characteristics of the institutions. These data are used by policy makers, planners, researchers, and others in the health community to monitor changes in the use of health care resources, to monitor specific diseases, and to examine the impact of new medical technologies, to mention a few.

TABLE 5-3 Surveys Included in the National Health Care Survey's System

National Ambulatory Medical Care Survey
National Employer Health Insurance Survey
National Health Provider Inventory
National Home and Hospice Care Survey
National Hospital Ambulatory Medical Care Survey
National Hospital Discharge Survey
National Nursing Home Survey
National Survey of Ambulatory Surgery

Two of the participating surveys are of particular relevance for the study of health care resources utilization in relation to sleep disorders: the National Ambulatory Medical Care Survey and the National Hospital Discharge Survey.

The National Ambulatory Medical Care Survey

The National Ambulatory Medical Care Survey, which has been conducted annually since 1989, is a national survey designed to meet the need for objective, reliable information about the provision and use of ambulatory medical care services in the United States. Findings are based on a sample of visits to non-federally employed office-based physicians who are primarily engaged in direct patient care. Specially trained interviewers visit the physicians prior to their participation in the survey in order to provide them with survey materials and instruct them on how to complete the forms. Data collection from the physician, rather than from the patient, provides an analytic base that expands information on ambulatory care collected through other NCHS surveys. Each physician is randomly assigned to a 1-week reporting period. During this period, data for a systematic random sample of visits are recorded by the physician or office staff on an encounter form provided for that purpose. Data are obtained on patients' symptoms, physicians' diagnoses, and medications ordered or provided. The survey also provides statistics on the demographic characteristics of patients and services provided, including information on diagnostic procedures, patient management, and planned future treatment.

The National Hospital Discharge Survey

The National Hospital Discharge Survey (NHDS), which has been conducted annually since 1965, is a national probability survey designed to provide information on characteristics of inpatients discharged from non-

federal short-stay hospitals in the United States. The NHDS collects data from a sample of approximately 270,000 inpatient records acquired from a national sample of about 500 hospitals. Only hospitals with an average length of stay of fewer than 30 days for all patients, general hospitals, or children's general hospitals are included in the survey. However, the NHDS excludes data from a number of hospitals, including federal, military, and Veterans Affairs (VA) hospitals; hospital units of institutions (such as prison hospitals); and hospitals with fewer than six beds staffed for patient use. The data includes information related to the personal characteristics of the patient—age, sex, race, ethnicity, marital status, expected sources of payment, and diagnoses and procedures coded to the *International Classification of Diseases, 9th Revision, Clinical Modification*. It also includes administrative items such as admission and discharge dates (which allow calculation of length of stay). Annually, data from the NHDS are made available to the public. As an example of the amount of data available in this survey, the estimated number of all listed sleep disorders diagnoses in NHDS in 2003 was 322,000. Although the NHDS excludes information obtained through VA hospitals, there is a similar database provided by the VA that has been used to examine the association of psychiatric disorders and sleep apnea (Sharafkhaneh et al., 2005).

Data from these surveys could be used to monitor prevalence of complaints related to sleep disorders; trends in sleep-related diagnosis and services; characteristics of patients, characteristics of health care providers; use of medical technology and how use differs according to region or patients' access to care; emergence of alternative care sites; and medication use in ambulatory care settings.

Behavioral Risk Factor Surveillance System

Funded by CDC, the Behavioral Risk Factor Surveillance System complements the NCHS national surveys by providing state-specific data on prevalence of the major behavioral risks among adults associated with premature morbidity and mortality. The main objective is to collect data on actual behaviors, rather than on attitudes or knowledge, that would be especially useful for planning, initiating, supporting, and evaluating health promotion and disease prevention programs at the state and local levels.

The Behavioral Risk Factor Surveillance System is an annual telephone survey (based on random digit dialing) in each participating state. The telephone surveys methodology was chosen not only because of cost advantages but also because telephone surveys were considered especially desirable at the state and local level, where the necessary expertise and resources for conducting area probability sampling for in-person household interviews were not likely to be available.

The survey started in 1984 with 15 participating states. By 1994, all states, the District of Columbia, and three territories were participating. Although the survey was designed to collect state-level data, a number of states from the outset stratified their samples to allow them to estimate prevalence for regions within their respective states. The CDC developed a standard core questionnaire for states to use to provide data that could be compared across states.

The emergence of telemarketing and increasing use of mobile phones and automatic answering systems resulted in dwindling response rates over the last few years. However it remains as the only state-specific source of health-related data nationwide. There are currently no sleep-related questions in Behavioral Risk Factor Surveillance System.

Medical Expenditure Panel Survey

Funded by the Agency for Healthcare Research and Quality, the Medical Expenditure Panel Survey is a national probability survey designed to continually provide policy makers, health care administrators, businesses, and others with timely, comprehensive information about health care use and costs in the United States, and to improve the accuracy of their economic projections. The survey began in 1977 and comprises three component surveys: the Household Component, the Medical Provider Component, and the Insurance Component. The Household Component provides a variety of measures of health status, health insurance coverage, health care use and expenditures, and sources of payment for health services. The Medical Provider Component covers hospitals, physicians, and home health care providers and is meant to estimate the expenses of people enrolled in health maintenance organizations and other types of managed care plans. Finally the Insurance Component is used to analyze the behavior and choices made with respect to health care use and spending, as well as the amount, types, and costs of health insurance available to Americans through their workplace.

Medicare Current Beneficiary Survey

Funded by Centers for Medicare and Medicaid Services, the Medicare Current Beneficiary Survey is a continuous, multipurpose survey of a nationally representative sample of aged, disabled, and institutionalized Medicare beneficiaries. The Medicare Current Beneficiary Survey is the only comprehensive source of information on the health status, health care use and expenditures, health insurance coverage, and socioeconomic and demographic characteristics of the entire spectrum of Medicare beneficiaries. The purpose of the survey is to determine expenditures and sources of payment

for all services used by Medicare beneficiaries; to establish all types of health insurance coverage and relate coverage to sources of payment; and to trace changes over time, such as health status, and the impacts of programmatic changes. It includes survey data on measures of health status and access to care that are linked to the physicians and hospital claims data. The survey was initiated in 1991 and is designed to support both cross-sectional and longitudinal analysis. Data are collected through interviews that take place over 4-month intervals. Each interview includes questions regarding the household composition; an accounting of the individual's health insurance coverage; a review of an individual's health care utilization in the period since the last interview; details about each type of service, provider characteristics, and medicines prescribed; and a detailed account of charges and payments associated with these health care events. The interview data are linked to Medicare claims.

Youth Risk and Behavior Survey

The Youth Risk Behavior Surveillance System includes national, state, and local school-based surveys of representative samples of 9th- through 12th-grade students (National Center for Chronic Disease Prevention and Health Promotion, 2005). These surveys are conducted every 2 years, usually during the spring semester. The national survey, conducted by CDC, provides data representative of high school students in public and private schools in the United States. The state and local surveys, conducted by departments of health and education, provide data representative of the state or local school district. The Risk Behavior Surveillance System was developed in 1990 to monitor priority health risk behaviors that contribute markedly to the leading causes of death, disability, and social problems among youth and adults in the United States. These behaviors, often established during childhood and early adolescence, include: tobacco use, dietary behaviors, physical activity, alcohol and other drug use, sexual behaviors, and behaviors that contribute to unintentional injuries and violence. Despite the importance of sleep deprivation and other sleep disorders in young adolescents (see Chapter 3), no questions on sleep and sleep behaviors have ever been included in the survey.

Process for Inclusion of New Components in Surveys

One impediment for the addition of greater sleep-related content in surveillance and monitoring instruments is the process required to have new components added. In addition to a high standard of scientific merit, inclusion of new components also often requires specific sponsorship. The

following is a description of the criteria for adding components or questions to NHANES. Other surveys and monitoring instruments have similar requirements.

Criteria for Adding Components to NHANES

Criteria for adding components or questions to NHANES and the NHIS are based on scientific merit, public health importance, costs, sponsorship, lead time, feasibility and logistics in the context of the rest of the survey components, priority ranking in relation to competing components, and survey burden.

NHANES runs in 2-year cycles and is governed by an internal committee formed by NCHS leadership, epidemiologists, statisticians, and physicians. Every 2 years, this committee requests proposals for adding components to the upcoming 2-year cycle, including both questionnaire components and mobile examination center exams. Proposals are received through a competitive bidding process and are expected to include detailed rationale for the public health relevance of the proposal, eligibility criteria (e.g., age, gender eligibility), detailed estimates of costs, personnel needs, amount of time required to do the exam, needs for laboratory or other type of equipment, statistical power estimates, quality assurance/quality control procedures, and the availability of external funds to subsidize the additional component. The committee then makes a preliminary determination as to its suitability before it reviews the proposal. Proposals under consideration are then examined by a team of NCHS personnel and proponents to carefully study and work out all the details and logistics of the implementation of the new exam.

New components to the exam are typically introduced for a single 2-year cycle, sometimes for multiple cycles (e.g., the sleep questionnaire is introduced for two cycles from 2005 to 2008). Eventually components are rotated off when sufficient data and sample size are acquired; some exams may be rescheduled at a later date in order to monitor changes and trends overtime. Other NCHS surveys follow similar procedures for review of added components with a few differences.

Both public and private organizations are eligible to propose new components to add to the NHANES and other NCHS surveys. Federal, state, or local government agencies can provide funds to the NCHS to cofinance the costs of the proposed additions. For example, the sleep questions on NHANES are sponsored by the NHLBI. Nonprofit organizations and private companies can also make proposals but cannot provide funds to the NCHS; cosponsorship from private industry, however, can occur through money deposited in the CDC foundation.

Recommendation 5.3: The Centers for Disease Control and Prevention and National Center on Sleep Disorders Research should support additional surveillance and monitoring of sleep patterns and sleep disorders.

The Centers for Disease Control and Prevention, working with the National Center on Sleep Disorders Research, should support the development and expansion of adequate surveillance and monitoring instruments designed to examine the American population's sleep patterns and the prevalence and health outcomes associated with sleep disorders.

REFERENCES

- AASM (American Academy of Sleep Medicine). 2005. *MedSleep*. [Online]. Available: http://www.aasmnet.org/MedSleep_Home.aspx [accessed December 17, 2005].
- ACGME (Accreditation Council of Graduate Medical Education). 2005a. *Program Requirements for Residency Education in Neurology*. [Online]. Available: http://www.acgme.org/acWebsite/downloads/RRC_progReq/180pr105.pdf [accessed March 22, 2006].
- ACGME. 2005b. *Residency Review Committees for Sleep Medicine*. [Online]. Available: http://www.acgme.org/acWebsite/downloads/RRC_PIF/520pif2_0405.doc [accessed December 16, 2005].
- American Board of Otolaryngology. 2006. *Otolaryngology Training Exam*. [Online]. Available: <http://www.aboto.org/blueprint.pdf> [accessed January 10, 2006].
- American Board of Pediatrics. 2006. *General Pediatrics Examination*. [Online]. Available: <http://www.abp.org/> [accessed January 10, 2006].
- American Board of Psychiatry and Neurology. 2006. *Psychiatry and Neurology Examination*. [Online]. Available: http://www.abpn.com/certification/neuro-neuro_items.html [accessed January 10, 2006].
- American Thoracic Society. 2005. Curriculum and competency assessment tools for sleep disorders in pulmonary fellowship training programs. *American Journal of Respiratory and Critical Care Medicine* 172(3):391–397.
- Banno K, Kryger MH. 2004. Factors limiting access to services for sleep apnea patients. *Sleep Medicine Reviews* 8(4):253–255.
- Buboltz WC, Brown F, Soper B. 2001. Sleep habits and patterns of college students: A preliminary study. *Journal of the American College of Health* 50(3):131–135.
- Buyse DJ, Barzansky B, Dinges D, Hogan E, Hunt CE, Owens J, Rosekind M, Rosen R, Simon F, Veasey S, Wiest F. 2003. Sleep, fatigue, and medical training: Setting an agenda for optimal learning and patient care. *Sleep* 26(2):218–225.
- CDC (Centers for Disease Control and Prevention). 1996. *Sudden Infant Death Syndrome—United States, 1983–1994*. [Online]. Available: <http://www.cdc.gov/mmwr/preview/mmwrhtml/00043987.htm> [accessed November 29, 2005].
- CDC. 2006. *Physical Activity for Everyone*. [Online]. Available: <http://www.cdc.gov/nccdphp/dnpa/physical/index.htm> [accessed January 6, 2006].
- Culpepper L. 2002. Generalized anxiety disorder in primary care: Emerging issues in management and treatment. *Journal of Clinical Psychiatry* 63(suppl 8):35–42.
- Dahl RE, Holttun J, Trubnick L. 1994. A clinical picture of child and adolescent narcolepsy. *Journal of the American Academy of Child and Adolescent Psychiatry* 33(6):834–841.

- Dement WC, Vaughn C. 1999. *The Promise of Sleep: The Scientific Connection Between Health, Happiness, and a Good Nights Sleep*. London: Macmillian.
- Dusselier L, Dunn B, Wang Y, Shelley MC II, Whalen DF. 2005. Personal, health, academic, and environmental predictors of stress for residence hall students. *Journal of the American College of Health* 54(1):15–24.
- Dzaja A, Arber S, Hislop J, Kerkhofs M, Kopp C, Pollmacher T, Polo-Kantola P, Skene DJ, Stenuit P, Tobler I, Porkka-Heiskanen T. 2005. Women's sleep in health and disease. *Journal of Psychiatric Research* 39(1):55–76.
- Engstrom CA, Strohl RA, Rose L, Lewandowski L, Stefanek ME. 1999. Sleep alterations in cancer patients. *Cancer Nursing* 22(2):143–148.
- Falvo D. 2005. *Medical and Psychosocial Aspects of Chronic Illness and Disability*. 3rd ed. Sudbury, MA: Jones and Bartlett.
- Federman DD. 2003. Competency-based goals for sleep and chronobiology in undergraduate medical education. *Sleep* 26(3):251.
- Fenn KM, Nusbaum HC, Margoliash D. 2003. Consolidation during sleep of perceptual learning of spoken language. *Nature* 425(6958):614–616.
- Gais S, Plihal W, Wagner U, Born J. 2000. Early sleep triggers memory for early visual discrimination skills. *Nature Neuroscience* 3(12):1335–1339.
- Guilleminault C, Pelayo R. 1998. Narcolepsy in prepubertal children. *Annals of Neurology* 43(1):135–142.
- Haponik E, Camp G. 1994. I snored: A simple sleep history for clinicians. *American Journal of Respiratory and Critical Care Medicine* 149(A53).
- Haponik EF, Frye AW, Richards B, Wymer A, Hinds A, Pearce K, McCall V, Konen J. 1996. Sleep history is neglected diagnostic information. Challenges for primary care physicians. *Journal of General Internal Medicine* 11(12):759–761.
- Harding SM, Berner ES. 2002. Developing an action plan for integrating sleep topics into the medical school curriculum. *Sleep and Breathing* 6(4):155–160.
- Hossain JL, Shapiro CM. 2002. The prevalence, cost implications, and management of sleep disorders: An overview. *Sleep and Breathing* 6(2):85–102.
- IOM (Institute of Medicine). 2002. *Speaking of Health: Assessing Health Communication Strategies for Diverse Populations*. Washington, DC: The National Academies Press.
- Kapur V, Strohl KP, Redline S, Iber C, O'Connor G, Nieto J. 2002. Underdiagnosis of sleep apnea syndrome in U.S. communities. *Sleep and Breathing* 6(2):49–54.
- Kemp JS, Livne M, White DK, Arfken CL. 1998. Softness and potential to cause rebreathing: Differences in bedding used by infants at high and low risk for sudden infant death syndrome. *Journal of Pediatrics* 132(2):234–239.
- Lack LC. 1986. Delayed sleep and sleep loss in university students. *Journal of the American College of Health* 35(3):105–110.
- Lee KA, Landis C, Chasens ER, Dowling G, Merritt S, Parker KP, Redeker N, Richards KC, Rogers AE, Shaver JF, Umlauf MG, Weaver TE. 2004. Sleep and chronobiology: Recommendations for nursing education. *Nursing Outlook* 52(3):126–133.
- Meadows R. 2005. *The "Negotiated Night:" An Embodied Conceptual Framework for the Sociological Study of Sleep*. Oxford: Blackwell.
- Mehlman M. 2001. Employee/employer interactions and responsibilities with special reference to genetically related sleep disorders. *Sleep and Breathing* 5(3):153–161.
- Miller NL, Shattuck LG. 2005. Sleep patterns of young men and women enrolled at the United States Military Academy: Results from year 1 of a 4-year longitudinal study. *Sleep* 28(7):837–841.
- Moore PJ, Adler NE, Williams DR, Jackson JS. 2002. Socioeconomic status and health: The role of sleep. *Psychosomatic Medicine* 64(2):337–344.

- National Center for Chronic Disease Prevention and Health Promotion. 2005. *YRBS: Youth Risk Behavior Surveillance System*. [Online]. Available: <http://www.cdc.gov/HealthyYouth/yrbs/index.htm> [accessed December 18, 2005].
- National Center for Health Statistics, National Health Interview Survey. 2004. *Percentage of Adults Who Reported an Average of <6 Hours of Sleep per 24-Hour Period, by Sex and Age Group*. [Online]. Available: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5437a7.htm> [accessed November 14, 2005].
- NHLBI (National Heart, Lung, and Blood Institute). 2003a. *National Sleep Disorders Research Plan, 2003*. Bethesda, MD: National Institutes of Health.
- NHLBI. 2003b. *Sleep, Sleep Disorders, and Biological Rhythms: NIH Curriculum Supplement Series, Grades 9-12*. Colorado Springs, CO: Biological Sciences Curriculum Study.
- NHLBI. 2004. *Be a Star Sleep* (Student and Teacher Guide Supplement). New York: Time, Inc.
- NHLBI. 2005a. *National High Blood Pressure Education Program*. [Online]. Available: http://www.nhlbi.nih.gov/about/nhbpep/nhbp_pd.htm [accessed November 22, 2005].
- NHLBI. 2005b. *Garfield Star Sleeper*. [Online]. Available: <http://www.nhlbi.nih.gov/health/public/sleep/starslp/> [accessed December, 2005].
- NHLBI. 2006. *Your Guide to Healthy Sleep*. [Online]. Available: http://www.nhlbi.nih.gov/health/public/sleep/healthy_sleep.htm [accessed May 27, 2006].
- NICHHD (National Institute of Child Health and Human Development). 2003. *SIDS rate and sleep position 1998-2003*. [Online]. Available: http://www.nichd.nih.gov/sids/SIDS_rate_backsleep_03.pdf [accessed November 18, 2005].
- Orr WC, Stahl ML, Dement WC, Reddington D. 1980. Physician education in sleep disorders. *Journal of Medical Education* 55(4):367-369.
- Owens J. 2005. Introduction to special section: NIH Sleep Academic Award program. *Sleep Medicine* 6(1):45-46.
- Owens JA, Dalzell V. 2005. Use of the "BEARS" sleep screening tool in a pediatric residents' continuity clinic: A pilot study. *Sleep Medicine* 6(1):63-69.
- Papp KK, Strohl KP. 2005. The effects of an intervention to teach medical students about obstructive sleep apnea. *Sleep Medicine* 6(1):71-73.
- Pilcher JJ, Ginter DR, Sadowsky B. 1997. Sleep quality versus sleep quantity: Relationships between sleep and measures of health, well-being and sleepiness in college students. *Journal of Psychosomatic Research* 42(6):583-596.
- Punjabi NM, Bandeen-Roche K, Young T. 2003. Predictors of objective sleep tendency in the general population. *Sleep* 26(6):678-683.
- Reynolds CF III, Adler S, Kanter SL, Horn JP, Harvey J, Bernier GM Jr. 1995. The undergraduate medical curriculum: Centralized versus departmentalized. *Academy of Medicine* 70(8):671-675.
- Roccella E. 2002. The contributions of public health education toward reduction of cardiovascular disease mortality: Experiences from the National High Blood Pressure Education Program. In: Hornik R, ed. *Public Health Communication: Evidence for Behavior Change*. Mahwah, NJ: Lawrence Erlbaum. Pp. 73-84.
- Rosen GM, Harris I, Mahowald MW. 2005. Objective structured clinical examinations (OSCE) for sleep. *Sleep Medicine* 6(1):75-80.
- Rosen RC, Rosekind M, Rosevear C, Cole WE, Dement WC. 1993. Physician education in sleep and sleep disorders: A national survey of U.S. medical schools. *Sleep* 16(3):249-254.
- Rosen R, Mahowald M, Chesson A, Doghramji K, Goldberg R, Moline M, Millman R, Zammit G, Mark B, Dement W. 1998. The Taskforce 2000 Survey on Medical Education in Sleep and Sleep Disorders. *Sleep* 21(3):235-238.
- Sateia MJ, Reed VA, Christian JG. 2005. The Dartmouth Sleep Knowledge and Attitude Survey: Development and validation. *Sleep Medicine* 6(1):47-54.

- Schoenborn CA. 1986. Health habits of U.S. adults, 1985: the "Alameda 7" revisited. *Public Health Report* 101(6):571–580.
- Sharafkhaneh A, Giray N, Richardson P, Young T, Hirshkowitz M. 2005. Association of psychiatric disorders and sleep apnea in a large cohort. *Sleep* 28(11):1405–1411.
- Siegel M. 2002. The effectiveness of state-level tobacco control interventions: A review of program implementation and behavioral outcomes. *Annual Review of Public Health* 23:45–71.
- Stickgold R, James L, Hobson JA. 2000. Visual discrimination learning requires sleep after training. *Nature Neuroscience* 3(12):1237–1238.
- Strohl KP, Veasey S, Harding S, Skatrud J, Berger HA, Papp KK, Dunagan D, Guilleminault C. 2003. Competency-based goals for sleep and chronobiology in undergraduate medical education. *Sleep* 26(3):333–336.
- Taylor B. 1993. Unconsciousness and society: The sociology of sleep. *International Journal of Politics, Culture, and Society* 6(3):463–474.
- U.S. Congress, Senate. 1993. *National Institutes of Health Revitalization Act of 1993*. 103rd Cong., S.104:285b-7.
- Walker MP, Brakefield T, Hobson JA, Stickgold R. 2003. Dissociable stages of human memory consolidation and reconsolidation. *Nature* 425(6958):616–620.
- Warner KE. 1981. Cigarette smoking in the 1970s: The impact of the antismoking campaign on consumption. *Science* 211(4483):729–731.
- Williams SJ. 2002. Sleep and health: Sociological reflections on the dormant society. *Health (N Y)* 6(2):173–200.
- Willinger M. 1995. SIDS prevention. *Pediatric Annals* 24(7):358–364.
- Wyatt JK. 2004. Delayed sleep phase syndrome: Pathophysiology and treatment options. *Sleep* 27(6):1195–1203.
- Zozula R, Rosen RC, Jahn EG. 2005. Recognition of sleep disorders in a community-based setting following an educational intervention. *Sleep Medicine* 6(1):55–61.

6

Ensuring Adequate Diagnosis and Treatment: Access, Capacity, and Technology Development

CHAPTER SUMMARY *Millions of individuals suffering from sleep disorders remain undiagnosed and untreated. Most American communities do not have adequate health care resources to meet the clinical demands. Further, the current diagnostic and therapeutic capacity is not sufficient for the present demand, let alone the predicted increase in demand arising from the proposed public education campaign. Thus, additional technology development is required. Based on estimates of the prevalence of sleep disorders, millions of individuals are undiagnosed and untreated. As awareness increases, greater investment in the development and validation of new diagnostic and therapeutic technologies will be required to meet the anticipated demand. Numerous technological advances have enhanced the feasibility of portable diagnosis and treatment, but they have not been fully evaluated and validated. Therefore, the committee urges the evaluation and validation of existing diagnostic and therapeutic technologies, as well as the development of new technologies.*

Increased awareness among the general public and health care practitioners will present numerous challenges to existing health care providers and researchers who are already stretched too thin. Therefore, as described in the following sections, development and improved capacity through technology development is required.

An increased recognition of sleep disorders has resulted in an increase in demand. In a 3-year period over the late 1990s, demand for a sleep test doubled in the United States (Pack and Gurubhagavatula, 1999). In France the number of patients diagnosed and receiving continuous positive airway pressure (CPAP) treatment is annually increasing by 20 percent (Gagnadoux et al., 2002). Demand has been accompanied by improved patient access to physicians and other clinicians trained in sleep medicine and to facilities where clinical sleep tests, polysomnograms, can be performed. There are currently an estimated 1,292 sleep centers or laboratories in the United States, 39 percent of which were accredited by the American Academy of Sleep Medicine (AASM) (Tachibana et al., 2005). However, resources have not kept up with demand. For example, 80 to 90 percent of obstructive sleep apnea (OSA) cases remain undiagnosed and untreated, which increases the burden of this disorder (Kapur et al., 2002). Narcolepsy, too, is infrequently detected (Singh et al., 2005), but precise rates of under diagnosis are not available because this condition is less common. Similarly, there is poor recognition and treatment of insomnia (Benca, 2005), as well as poor communication between patient and physician. Thus, even with a growth in resources, this issue is of significant importance to the millions of individuals suffering from sleep disorders.

DEVELOPING PORTABLE DIAGNOSTIC TOOLS

Polysomnography, the “gold standard” procedure for the diagnosis of most sleep disorders, is not readily available for everyone who needs it. These procedures employ simultaneous monitoring of numerous physiological parameters including brain wave activity, eye movements, muscle activity (chin and legs), heart rate, body position, and respiratory variables, including oxygen saturation. The test is typically performed overnight in a sleep laboratory with a technician in attendance, requiring an individual to sleep in the laboratory. Thus, this procedure necessitates facilities that accommodate overnight testing (beds and monitoring areas), highly sophisticated equipment, trained staff who are willing to work night shifts, and physicians trained in sleep medicine.

Although there may currently be cost-effective ways to manage sleep disorder, the capacity does not currently exist to diagnose and treat all individuals. Most American communities do not have adequate health care resources to meet the clinical demands of treating the large number of

patients with sleep disorders (Banno and Kryger, 2004; Tachibana et al., 2005). In many health care systems and communities, waiting lists may be as long as 10 weeks (Rodsutti et al., 2004), with even longer waiting times in certain systems such as Veterans Affairs Medical Centers (Sharafkhaneh et al., 2004). Although this is not a problem that is unique to the field, long wait lists cause significant delays in diagnosing and treating individuals (Banno and Kryger, 2004). This is of particular concern for individuals with sleep disorders that lead to increased chance of injury. For example, undiagnosed severe OSA can lead to death or serious harm of self or others due to crashes (George, 2001). Further, long wait times contribute to high no-show rates that in turn increases the length of the wait-lists (Callahan and Redmon, 1987; Olivares, 1990). This also may decrease market share (Christl, 1973; Antle and Reid, 1988). It has been estimated that sleep apnea alone, a diagnosis that necessitates polysomnography to meet current criteria set out by third-party payers, annually requires at least 2,310 polysomnograms per 100,000 population to address the demand for diagnosis and treatment (Flemons et al., 2004). However, on average, only 427 polysomnograms per 100,000 population are performed each year in the United States, a level far below the need. In fact, 32 states annually perform less than 500 polysomnograms (Tachibana et al., 2005). Only Maryland annually performs more than 1,000. This large geographic variability in levels of sleep services is not explained by Medicare reimbursement rates, race, or distribution of OSA risk factors in these areas (Tachibana et al., 2005). Further, such geographical variability suggests the need for more standardized approaches for diagnosis and disease management.

Limitations in providing overnight diagnostic sleep laboratory services are attributed to a number of factors. Direct costs associated with having a polysomnogram performed (Chapter 4) are high. In addition, there are high expenses to sleep laboratories, including costs related to the initial investment in equipment (hardware and software) and information technology needed to manage large amounts of digital data. There are considerable personnel costs related to dedicating one to two trained technicians to each patient for a 10- to 12-hour period (for orientation, hookup, and minute-by-minute monitoring) and for scoring of studies (2 to 3 hours per study), overhead for space (which traditionally has used in-patient hospital space and more recently has used space in upscale hotels that contract with health care organizations to provide rooms or floors that serve as “community-based sleep laboratories”), and costs related to consumable supplies used for monitoring. Most insurers require sleep laboratories to be supervised by physicians or other clinicians certified by the American Academy of Sleep Medicine. In addition, many patients are reluctant to undergo somewhat intrusive monitoring and to spend one or more nights away from home. The latter is of special concern to individuals with home care (of their chil-

dren or parents) responsibilities. These factors have contributed to an interest in developing portable, and perhaps simpler, less costly and less intrusive devices that can be used in a patient's own home, with the goals of improving access and decreasing the cost of sleep studies.

The Potential of Developing Portable Sleep Monitoring

Numerous technological advances have enhanced the feasibility of portable monitoring. These include miniaturization of recording components, efficiencies of digital data storage, remote monitoring capabilities (allowing centrally based technicians to monitor signals at home via wireless or modem communications), and development of new physiological sensors. Advances have been such that essentially the same data that are collected using full polysomnography in the laboratory can be collected in the home with monitors that weigh less than 300 grams. Large-scale epidemiological studies have demonstrated the feasibility of such multichannel recordings done in children and in middle-aged and elderly individuals (Goodwin et al., 2003; Redline et al., 1998). Recent experience in a community sample of almost 3,000 older men, a large percentage of whom had OSA and periodic limb movements, indicates that this approach can yield high quality data in 97 percent of studies performed (personal communication, S. Redline, Case Western Reserve University School of Medicine, December 15, 2005). The improvement in the high quality of data in this study compared to previous studies is largely due to technological advances. A study comparing the quality of data obtained from an in-home to an in-laboratory study demonstrates comparable quality and evidence of slightly less stage 1 sleep (i.e., lighter sleep) in the home, suggesting that patients may sleep better and have more representative sleep at home (Iber et al., 2004). The apnea-hypopnea index (AHI) determined using the two methods were highly correlated; however, a Bland Altman plot showed that at lower AHIs, the AHI tended to be lower in the laboratory than at home, and at higher AHIs, the AHI was higher in the laboratory than home. The latter phenomenon was thought to relate to positional differences in apnea severity, with severely affected patients probably spending more time on their back when sleeping in the typical hospital bed than when studied at home. However, although recent studies suggest low failure rates, there may be significant differences in the failure rates of unattended monitoring in less controlled settings. Thus examination of the efficacy of such technologies should be performed in less controlled settings, as may occur in clinical practice.

Despite the promise of this technology, such comprehensive monitoring, even at home, is probably as burdensome to patients as when performed in the laboratory, requires a technician to travel to the patient's

home to set up and retrieve the units, and has a higher failure rate due to all the vagaries of using many sensors in an unattended manner. Failure rates between 5 to 20 percent have been reported for ambulatory diagnostic devices (Redline et al., 1998; Whitney et al., 1998; Fry et al., 1998; Mykytyn et al., 1999; Portier et al., 2000); however, since these reports were released there have been many technological improvements. A formal cost-benefit analysis of 12 to 14 multichannel in-home monitoring compared to in-laboratory monitoring has not been performed. Thus, there is interest in use of simpler technology with sufficient predictive value to be used in decision making.

Technological advances also have led to the incorporation and packaging of various groups of sensors, many novel, designed to provide simpler means for quantifying airflow limitation or breathing effort, oxygen desaturation, snoring sounds, movement, heart rate, blood pressure, and vascular tone variability.

Several of these devices are designed to primarily provide estimates of sleep and wake time over 24-hour periods, such as wrist actigraphs (i.e., a movement detector coupled with software that uses movement patterns to provide estimated sleep and wake times) (Ancoli-Israel et al., 1997). These are used more often in research than in clinical settings, although clinically they have been used to enhance evaluation of sleep-wake disorders. These devices provide estimates of sleep time that correlate moderately well to polysomnography-based estimates; however, in certain high-risk subgroups, such as children with attention-deficit/hyperactivity disorder or sleep apnea, they may perform less well (Bader et al., 2003).

A detailed review of different ambulatory technologies for sleep apnea measurement was recently performed (Flemons et al., 2003; Tice, 2005). Most devices have been designed to screen or diagnose sleep apnea. Several novel portable devices that have been informed by a growing knowledge of physiological correlates of sleep apnea have been developed. A recent review by the AASM has identified the utility of measuring nasal pressure from a sensor placed in the outer nares, which accurately detects airflow limitation (Krieger et al., 2002), the sine qua non of OSA. Several devices combine this sensor with sensors that measure oxygen saturation, snoring, and other sleep apnea correlates. For example, a relatively simple device has been designed to measure nasal pressure, oximetry, head movement, and snoring with a head band containing these sensors that is placed around the forehead and can be self-applied without glue or skin preparation (Westbrook et al., 2005). The AHI derived using an early version of this device tested in both in-home and in-laboratory settings in a large sample showed sensitivities of 92 to 98 percent and specificities of 86 to 100 percent for identification of sleep apnea. An advantage of such technology includes its potential to easily measure sleep over two or more nights (enhancing reliability) and its potential reduced cost

(estimated at 30 to 50 percent of that of in-laboratory polysomnography). There has also been great interest in the use of completely novel sensors that have not been traditionally used in the sleep laboratory, but which are based on growing interests in the autonomic sequelae of sleep apnea. One such device measures peripheral artery tone from a sensor placed on the finger and has been shown to provide estimates of vascular flow, a measure that reflects variations in breathing and sleep-related arousals (Lavie et al., 2000). One wrist-worn device that uses this sensor in combination with sensors measuring oxygen saturation, heart rate, and movement has shown promising utility for sleep apnea detection. Preliminary data from one study showed a 95 percent sensitivity and 100 percent specificity (Pittman et al., 2004). Other studies have also supported this approach (Ayas et al., 2003), including results from a study of almost 100 individuals (Zou et al., 2006). Another exciting advance is the development of oximeters that are relatively resistant to movement artifact, thus improving the accuracy of such data in unattended settings (Barker, 2002).

CHALLENGES TO DEVELOPING AMBULATORY TECHNOLOGIES

Despite the promise of this technology, use of portable monitoring for diagnosis or management of sleep disorders has not yet been endorsed by any professional organization. Dozens of studies have been conducted that evaluate different aspects of technology use (ranging from evaluation of the accuracy of individual sensors to use in epidemiological studies to use in case identification); however, very few studies have met rigorous criteria for endorsement of a new diagnostic test, including comparison to a reference standard, blinded assessments, and use of large samples (Tice, 2005). Although development and evaluation of new and improved sleep monitors are much needed, the industry has failed to invest in conducting such rigorous studies. The National Institutes of Health (NIH) has invested in such assessments mostly through Small Business Innovation Research (SBIR) grants; however, between 2002 to 2005, only 17 SBIR grants were awarded to develop and evaluate new sleep technology, and many of these studies were designed to test feasibility (phase I) rather than efficacy.

There are several challenges to technology development and evaluation that may be fairly specific to sleep medicine. Challenges relate to the underlying uncertainty over: (1) which physiological signals best capture the stresses associated with sleep apnea and thus would most optimally identify patients who are either at increased risk for sleep apnea-related morbidity or who are most likely to require and respond to therapy; and (2) what threshold values, if any, for quantitative data derived from physiological monitoring best identify patients at risk or likely to respond to therapy. The collection of 12 or more channels of physiological data on sleep architec-

ture, cardiovascular responses, and disordered breathing potentially provides the clinician a comprehensive panel of data from which to make treatment decisions. The influences of reducing this panel of data on clinical decisions and short- and long-term disease management are unclear. Emerging data suggest that different sleep apnea-related outcomes may be differentially predicted by alternative indexes of physiological stress captured by polysomnography. One recent cross-sectional study, for example, showed that while indexes of overnight hypoxemia were most strongly associated with glucose impairment, the arousal index best predicted hypertension (Sulit et al., 2006). Thus, monitors that selectively record one set of physiological disturbances may be well suited for predicting some, but not all outcomes. Threshold values may also differ according to the physiological outcome of interest. For example, data from the Sleep Heart Health Study suggest that an increased prevalence of hypertension may be observed at a threshold AHI that is higher than the threshold associated with other cardiovascular manifestations (Nieto et al., 2000; Shahar et al., 2001). Such uncertainties hamper technological efforts at choosing sensor “packages” that are most clinically relevant and evaluation procedures that require clear consensus over affection status to determine sensitivity and specificity.

Implicit in the challenges noted above are the very limited available data that address the clinical utility of the most commonly considered reference standard of polysomnography, coupled with current practice that focuses on specific numbers obtained from this test to make specific diagnoses. However, the latter practice is actually not well supported by evidence, and there is much debate over which threshold levels define “disease” and what combinations of data should be used to construct each metric (Ryan et al., 1988; Redline and Sanders, 1999). Little available research has evaluated the specific contribution of polysomnography over information obtained by other clinical assessments, including history and examination. As mentioned, although multiple physiological variables are captured, there is no clear consensus on how these data are most optimally combined for case identification or for disease assessment. Historically, the field (including third-party insurers) have used a single metric such as the AHI for defining sleep apnea, or the periodic limb movement index (PLMI) for periodic limb movement disorder, defining disease by using a single cutoff value for each (e.g., AHI greater than 5 for sleep apnea or PLMI greater than 5 for periodic limb movement disorder). However, this approach, which emphasizes the centrality of a single number—and which is known to vary from night to night (Quan et al., 2002)—differs from that in other fields where data from physiological tests are used as one of many indices to gauge disease severity and to follow treatment responses, but are not used as the sole diagnostic instrument. For example, asthma, a common chronic inflammatory disease of the airways, is diagnosed predominantly

using a careful history; lung function tests are used to gauge disease severity and treatment responses and sometimes to help differentiate asthma from other respiratory conditions. The issues that plague equipment development and laboratory access in the sleep laboratory have not impeded the development of lung function laboratories. Rather, the development and accreditation of lung function laboratories and lung function equipment (including portable spirometers) are based on collecting reproducible data that meet physiological criteria for accuracy, independent of the role of such equipment as tools evaluated on their ability to independently classify disease status. It is recognized that the latter requires consideration of multiple factors, including symptoms, level of impairment, response to allergic and irritant triggers, and often empiric responses to therapeutic trials.

Other challenges relate to designing studies that specifically address a number of distinct potential applications of portable sleep monitoring. These include screening—which is often population-based, and intended to detect cases independent of symptoms; clinical case definition—identification of cases among patients referred because of health concerns; disease management in which sleep monitoring provides quantitative data on progression or regression of disease severity; and epidemiological studies—in which sleep monitoring is used to provide a quantitative assessment of a physiological exposure or outcome. It is important that any given evaluation study of new technologies be designed to address a specific question or related series of questions.

Scoring and Processing of Sleep Studies

Current scoring approaches use a system of epoch by epoch scoring (30 seconds per epoch) developed over 40 years ago when polysomnography used only paper-based systems based on analog data. This approach is recognized to be both labor-intensive and time-consuming. Further, reliance on human scorers using visual pattern recognition requires intensive and ongoing training to achieve high reliability (Whitney et al., 1998), which may be lower than that potentially attained by automated methods (which also have their limitations). Visual scoring also may not maximally utilize the spectral components of the electrophysiological data, which may provide useful information on sleep architecture. Furthermore, there is a shortage of trained sleep technicians. Currently there are only 2,198 certified technicians to monitor and score sleep tests, far below the need (Association of Polysomnographic Technologists, 1999). Recognizing these issues, the AASM convened a task force in 2004 to reassess current scoring approaches, critically evaluate both sensors and scoring algorithms, and update scoring approaches as appropriate to include digital analysis of electrophysiological data. This report, scheduled

for release in 2006, should provide important advances for the diagnosis of chronic sleep loss and sleep disorders.

Summary of Formal Evaluation Reviews

Three recent in-depth reviews have been performed to examine the effectiveness of portable monitoring devices (Ross et al., 2000; ATS, 2004; Tice, 2005). As described above, these reports were largely aimed at evaluating the literature regarding the accuracy of clinical diagnosis relative to reference in lab polysomnography, with some attempt at also evaluating the literature relative to cost-effectiveness and clinical prediction. In 1998, the Agency for Healthcare Research and Quality performed a literature review and meta-analysis on studies of portable monitoring for OSA. The review concluded that at the time there was insufficient evidence to make firm recommendations for use of portable monitoring for the diagnosis of sleep apnea (Ross et al., 2000).

An executive summary on the systematic review and practice parameters for portable monitoring in the investigation of suspected sleep apnea in adults was published in 2004 by an evidence review committee consisting of members from the American Thoracic Society, the American College of Chest Physicians, and the American Academy of Sleep Medicine (ATS, 2004; Flemons and Littner, 2003). In that summary, the following recommendations were made:

- Given the available data, the use of portable device was not recommended for general screening.
- The use of portable devices was not recommended in patients with comorbid conditions or secondary sleep complaints.
- The use of portable devices should require review of raw data by trained sleep specialists.

The review committee also recognized the need for further development of portable devices and suggested several goals for future research. It was found that most studies on portable monitoring were performed primarily on white males with OSA who had few comorbidities. The evidence review committee recommended that future studies should include more diverse populations, other than patients with sleep apnea, that are not subject to selection bias. Additional recommendations were that future studies should address clinical predictive algorithms in combination with portable monitoring in the diagnosis of sleep apnea, and study design should assess the cost-effectiveness and outcomes associated with different diagnostic and management strategies.

The California Technology Assessment Forum most recently evaluated the evidence that supported use of ambulatory devices over in-laboratory procedures for the purposes of diagnosing sleep apnea (Tice, 2005). The following five technology assessment criteria were identified:

- The technology must have final approval from government regulatory bodies.
- The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.
- The technology must improve health outcomes.
- The technical must be as beneficial as any established alternatives.
- The technology must be attainable outside of the investigational setting.

They determined that only the first two criteria had been met, but the last three were not. This review also identified the paucity of data regarding the “reference standard” (laboratory polysomnography) as improving health outcomes and suggested that a therapeutic trial of CPAP therapy may be a more efficient and clinically relevant approach than use of either in-home or in-laboratory sleep monitoring.

Evaluating Daytime Sleepiness

There is also a need to improve diagnostic procedures aiming at the quantification of excessive daytime sleepiness and the diagnosis of narcolepsy and hypersomnia. The current gold standard is the clinical Multiple Sleep Latency Test (MSLT), conducted after nocturnal polysomnography is performed (Littner et al., 2005). Sleepiness is considered consistent with hypersomnia or narcolepsy when a mean sleep latency less or equal to 8 minutes is observed (AASM, 2005). The observation of multiple sleep onset rapid eye movement (REM) periods (SOREMPs) during five naps is considered diagnostic for narcolepsy (see Chapter 3). Problematically however, the MSLT is sensitive to sleep deprivation and sleep-disordered breathing; thus, the test is often difficult to interpret. Population-based studies with the experimental MSLT, a modified version of the MSLT where mean sleep latency, but not SOREMP are measured, suggest that a large portion of the population has a short sleep latency (Kim and Young, 2005) and that the test correlates only partially with subjective measures of excessive daytime sleepiness. This has led to the revised diagnostic criteria that suggest that the MSLT should only be interpreted in the absence of sleep apnea and sufficient sleep prior to the MSLT (total sleep time equal to or greater than 6 hours) (AASM, 2005). Very limited clinical MSLT data are available in population samples, but data to date suggest that 3.9 percent of individuals may be positive for SOREMPs independent of daytime sleepiness (Singh et

al., 2005). Similarly, the Maintenance of Wakefulness Test (MWT), a test in which the subject is asked to try not to fall asleep in naps and sleep latency is measured, has been used to objectively measure alertness in drug trials but is not validated to demonstrate an ability to stay awake for patients at risk, for example in medicolegal cases and the evaluation of driving abilities (Littner et al., 2005).

As conducted, the MSLT and the MWT are time-consuming and expensive, and validation in the general population sample is lacking. How sleep apnea and prior sleep time in and outside the laboratory affects the occurrence of SOREMPs in MSLTs is not established. It is also unknown whether these tests may not be more valid after a night at home and verification of sleep with actigraphy or other procedures, a modification that would reduce cost in some cases. Finally, performance tests such as the psychomotor vigilance task, used commonly to evaluate performance after sleep deprivation, may have applications in this area (Dauvilliers and Buguet, 2005), especially if those tests can be adjusted to be used in ambulatory situations. Biochemical and imaging research aiming at discovering biomarkers of sleep debt and sleepiness is also needed.

Other Diagnostic Technologies

In addition to the development of ambulatory strategies, efforts are also currently under way to utilize other techniques to diagnose individuals who suffer chronic sleep loss or sleep disorders. These strategies include the development of genetic and biochemical tests for narcolepsy, magnetic resonance imaging (MRI) to visualize the upper airway in children with OSA, and acoustic reflectometry (a noninvasive ultrasound technique) of the upper airway to quantify anatomic obstruction of the upper airway in children (Mignot et al., 2002; Arens et al., 2003; Monahan et al., 2002; Donnelly et al., 2004; Abbott et al., 2004). Tests such as the standardized immobilization test or biochemical/imaging measures of brain iron metabolism are being developed to assist in the diagnosis and quantification of severity in restless leg syndrome (Allen and Earley, 2001; Garcia-Borreguero et al., 2004; Trenkwalder et al., 2005). Actigraphy and other methods are also used to estimate leg movement frequency in outpatients (Kazenwadel et al., 1995; Sforza et al., 2005). Video technologies may also be of value, especially in the diagnosis of individuals with night terrors. Finally, there is a need to establish novel procedures to objectively identify abnormalities in insomnia beyond the changes generally observed using sleep questionnaires, logs, and polysomnography (Roth and Drake, 2004). These may involve the use of spectral analysis (Perlis et al., 2001), microstructural cyclic alternating patterns analysis (Parrino et al., 2004), and functional neuroimaging (Drummond et al., 2004; Nofzinger, 2005).

The development of polysomnograms that are performed in a local hospital and telemonitored by a central sleep laboratory could allow for a single technician to monitor multiple studies from a central location. However, the reliability of these procedures varies (Gagnadoux et al., 2002).

FUTURE DIRECTIONS

Given the cumbersome nature and cost of the diagnosis and treatment of sleep disorders and sleep loss, the resultant inequities with regard to access, and in order to ensure future quality care, greater investment in the development of new, and validation of existing, diagnostic and therapeutic technologies is required. Improvement in portable monitoring techniques will likely enhance access to sleep diagnostic services. With the inadequate availability of sleep centers and sleep technicians, not only in the United States but more so worldwide, access to portable diagnostic screening procedures and streamlining initiation of treatment would clearly be advantageous. In particular, portable monitoring at level III (limited channel polysomnogram of four or more cardiopulmonary bioparameters) or level IV (testing of only one or two cardiopulmonary bioparameters) would help lower health costs and shorten waiting lists. In selected patient populations, portable monitoring in conjunction with inpatient split-night polysomnography or unattended autotitration of nasal CPAP could prove to be the most cost-effective and rational approach to most patients with a clinical profile for moderate to severe sleep apnea syndrome. Research in the design and evaluation of existing and novel diagnostic technologies is also needed in the area of insomnia, hypersomnia, and restless legs syndrome and periodic limb movements.

However, the rational application of technology needs to be coupled with the following:

- A reexamination of the role of diagnostic testing in case identification and disease management, clarifying optimal use of objective physiological monitoring data (including data obtained from portable monitors) in clinical diagnostic and management algorithms.
- Recognition that the development of new physiological monitoring tools needs to be guided by research that clarifies the short- and long-term clinical predictive information of specific channels (including responses to clinical interventions), or combinations of data. This should include consideration of the extent to which data from new technologies complement those from other techniques.
- Standardization of diagnostic and treatment criteria, language, and technologies.
- Investigation of how information from laboratory and portable diagnosis may interface as complementary rather than competitive technologies.

- Investment by industry and the NIH in rigorous evaluation and outcome studies that are designed to test specific questions regarding technology applications in improving the efficiency of screening, case identification, and disease management.
- Assessment of technologies utilizing indexes to examine their cost-effectiveness.
- Development of technologies keeping in mind that treatment of sleep disorders requires a chronic care management scheme (see Chapter 9).
- Specific efforts to develop and modify technologies for children.

Recommendation 6.1: The National Institutes of Health and the Agency for Healthcare Research and Quality should support the validation and development of existing and new diagnostic and therapeutic technologies.

The National Center on Sleep Disorders Research—working with the Trans-NIH Sleep Research Coordinating Committee, the Agency for Health Care Policy and Research, other federal agencies, and private industry—should support the evaluation and validation of existing diagnostic and therapeutic technologies. Further, development of new technologies such as ambulatory monitoring, biological markers, and imaging techniques should be vigorously supported.

REFERENCES

- AASM (American Academy of Sleep Medicine). 2005. *The International Classification of Sleep Disorders*. Westchester, IL: AASM.
- Abbott MB, Donnelly LF, Dardzinski BJ, Poe SA, Chini BA, Amin RS. 2004. Obstructive sleep apnea: MR imaging volume segmentation analysis. *Radiology* 232(3):889–895.
- Allen RP, Earley CJ. 2001. Restless legs syndrome: A review of clinical and pathophysiological features. *Journal of Clinical Neurophysiology* 18(2):128–147.
- Ancoli-Israel S, Clopton P, Klauber MR, Fell R, Mason W. 1997. Use of wrist activity for monitoring sleep/wake in demented nursing-home patients. *Sleep* 20(1):24–27.
- Antle DW, Reid RA. 1988. Managing service capacity in an ambulatory care clinic. *Hospital and Health Services Administration* 33(2):201–211.
- Arens R, McDonough JM, Corbin AM, Rubin NK, Carroll ME, Pack AI, Liu J, Udupa JK. 2003. Upper airway size analysis by magnetic resonance imaging of children with obstructive sleep apnea syndrome. *American Journal of Respiratory and Critical Care Medicine* 167(1):65–70.
- Association of Polysomnographic Technologists. 1999. *The APT Demographic, Salary, and Educational Needs Survey*. Lenexa, KS: APT.
- ATS (American Thoracic Society). 2004. Executive summary on the systematic review and practice parameters for portable monitoring in the investigation of suspected sleep apnea in adults. *American Journal of Respiratory and Critical Care Medicine* 169(10):1160–1163.

- Ayas NT, Pittman S, MacDonald M, White DP. 2003. Assessment of a wrist-worn device in the detection of obstructive sleep apnea. *Sleep Medicine* 4(5):435–442.
- Bader G, Gillberg C, Johnson M, Kadesjö B, Rasmussen P. 2003. Activity and sleep in children with ADHD. *Sleep* 26:A136.
- Banno K, Kryger MH. 2004. Factors limiting access to services for sleep apnea patients. *Sleep Medicine Reviews* 8(4):253–255.
- Barker SJ. 2002. “Motion-resistant” pulse oximetry: A comparison of new and old models. *Anesthesia and Analgesia* 95(4):967–972.
- Benca RM. 2005. Diagnosis and treatment of chronic insomnia: A review. *Psychiatry Services* 56(3):332–343.
- Callahan NM, Redmon WK. 1987. Effects of problem-based scheduling on patient waiting and staff utilization of time in a pediatric clinic. *Journal of Applied Behavioral Analysis* 20(2):193–199.
- Christl HL. 1973. Some methods of operations research applied to patient scheduling problems. *Medical Progress Through Technology* 2(1):19–27.
- Dauvilliers Y, Buguet A. 2005. Hypersomnia. *Dialogues in Clinical Neuroscience* 7(4):347–356.
- Donnelly LF, Shott SR, LaRose CR, Chini BA, Amin RS. 2004. Causes of persistent obstructive sleep apnea despite previous tonsillectomy and adenoidectomy in children with Down syndrome as depicted on static and dynamic cine MRI. *American Journal of Roentgenology* 183(1):175–181.
- Drummond SP, Smith MT, Orff HJ, Chengazi V, Perlis ML. 2004. Functional imaging of the sleeping brain: Review of findings and implications for the study of insomnia. *Sleep Medicine Reviews* 8(3):227–242.
- Flemons WW, Littner MR. 2003. Measuring agreement between diagnostic devices. *Chest* 124(4):1535–1542.
- Flemons WW, Littner MR, Rowley JA, Gay P, Anderson WM, Hudgel DW, McEvoy RD, Loubé DI. 2003. Home diagnosis of sleep apnea: A systematic review of the literature. An evidence review cosponsored by the American Academy of Sleep Medicine, the American College of Chest Physicians, and the American Thoracic Society. *Chest* 124(4):1543–1579.
- Flemons WW, Douglas NJ, Kuna ST, Rodenstein DO, Wheatley J. 2004. Access to diagnosis and treatment of patients with suspected sleep apnea. *American Journal of Respiratory and Critical Care Medicine* 169(6):668–672.
- Fry JM, DiPhillipo MA, Curran K, Goldberg R, Baran AS. 1998. Full polysomnography in the home. *Sleep* 21(6):635–642.
- Gagnadoux F, Pelletier-Fleury N, Philippe C, Rakotonanahary D, Fleury B. 2002. Home unattended vs hospital telemonitored polysomnography in suspected obstructive sleep apnea syndrome: A randomized crossover trial. *Chest* 121(3):753–758.
- Garcia-Borreguero D, Larrosa O, de la Llave Y, Granizo JJ, Allen R. 2004. Correlation between rating scales and sleep laboratory measurements in restless legs syndrome. *Sleep Medicine* 5(6):561–565.
- George CF. 2001. Reduction in motor vehicle collisions following treatment of sleep apnoea with nasal CPAP. *Thorax* 56(7):508–512.
- Goodwin JL, Kaemingk KL, Fregosi RF, Rosen GM, Morgan WJ, Sherrill DL, Quan SF. 2003. Clinical outcomes associated with sleep-disordered breathing in Caucasian and Hispanic children—the Tucson Children’s Assessment of Sleep Apnea Study (TuCASA). *Sleep* 26(5):587–591.
- Iber C, Redline S, Kaplan Gilpin AM, Quan SF, Zhang L, Gottlieb DJ, Rapoport D, Resnick HE, Sanders M, Smith P. 2004. Polysomnography performed in the unattended home versus the attended laboratory setting—Sleep Heart Health Study methodology. *Sleep* 27(3):536–540.

- Kapur V, Strohl KP, Redline S, Iber C, O'Connor G, Nieto J. 2002. Underdiagnosis of sleep apnea syndrome in U.S. communities. *Sleep and Breathing* 6(2):49–54.
- Kazenwadel J, Pollmacher T, Trenkwalder C, Oertel WH, Kohnen R, Kunzel M, Kruger HP. 1995. New actigraphic assessment method for periodic leg movements (PLM). *Sleep* 18(8):689–697.
- Kim H, Young T. 2005. Subjective daytime sleepiness: Dimensions and correlates in the general population. *Sleep* 28(5):625–634.
- Krieger J, McNicholas WT, Levy P, De Backer W, Douglas N, Marrone O, Montserrat J, Peter JH, Rodenstein D, European Respiratory Society Task Force. 2002. Public health and medicolegal implications of sleep apnoea. *European Respiratory Journal* 20(6):1594–1609.
- Lavie P, Schnall RP, Sheffy J, Shlitner A. 2000. Peripheral vasoconstriction during REM sleep detected by a new plethysmographic method. *Nature Medicine* 6(6):606.
- Littner MR, Kushida C, Wise M, Davila DG, Morgenthaler T, Lee-Chiong T, Hirshkowitz M, Daniel LL, Bailey D, Berry RB, Kapen S, Kramer M. 2005. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep* 28(1):113–121.
- Mignot E, Lammers GJ, Ripley B, Okun M, Nevsimalova S, Overeem S, Vankova J, Black J, Harsh J, Bassetti C, Schrader H, Nishino S. 2002. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. *Archives of Neurology* 59(10):1553–1562.
- Monahan KJ, Larkin EK, Rosen CL, Graham G, Redline S. 2002. Utility of noninvasive pharyngometry in epidemiologic studies of childhood sleep-disordered breathing. *American Journal of Respiratory and Critical Care Medicine* 165(11):1499–1503.
- Mykityn IJ, Sajkov D, Neill AM, McEvoy RD. 1999. Portable computerized polysomnography in attended and unattended settings. *Chest* 115(1):114–122.
- Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. 2000. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *Journal of the American Medical Association* 283(14):1829–1836.
- Nofzinger EA. 2005. Functional neuroimaging of sleep. *Seminars in Neurology* 25(1):9–18.
- Olivares VE. 1990. Scheduling strategies. *Radiology Management* 12(3):29–30.
- Pack AI, Gurubhagavatula I. 1999. Economic implications of the diagnosis of obstructive sleep apnea. *Annals of Internal Medicine* 130(6):533–534.
- Parrino L, Ferrillo F, Smerieri A, Spaggiari MC, Palomba V, Rossi M, Terzano MG. 2004. Is insomnia a neurophysiological disorder? The role of sleep EEG microstructure. *Brain Research Bulletin* 63(5):377–383.
- Perlis ML, Smith MT, Andrews PJ, Orff H, Giles DE. 2001. Beta/Gamma EEG activity in patients with primary and secondary insomnia and good sleeper controls. *Sleep* 24(1):110–117.
- Pittman SD, Ayas NT, MacDonald MM, Malhotra A, Fogel RB, White DP. 2004. Using a wrist-worn device based on peripheral arterial tonometry to diagnose obstructive sleep apnea: In-laboratory and ambulatory validation. *Sleep* 27(5):923–933.
- Portier F, Portmann A, Czernichow P, Vascaut L, Devin E, Benhamou D, Cuvelier A, Muir JF. 2000. Evaluation of home versus laboratory polysomnography in the diagnosis of sleep apnea syndrome. *American Journal of Respiratory and Critical Care Medicine* 162(3 Pt 1):814–818.
- Quan SF, Griswold ME, Iber C, Nieto FJ, Rapoport DM, Redline S, Sanders M, Young T. 2002. Short-term variability of respiration and sleep during unattended nonlaboratory polysomnography—the Sleep Heart Health Study. *Sleep* 25(8):843–849.

- Redline S, Sanders M. 1999. A quagmire for clinicians: When technological advances exceed clinical knowledge. *Thorax* 54(6):474–475.
- Redline S, Sanders MH, Lind BK, Quan SF, Iber C, Gottlieb DJ, Bonekat WH, Rapoport DM, Smith PL, Kiley JP. 1998. Methods for obtaining and analyzing unattended polysomnography data for a multicenter study. Sleep Heart Health Research Group. *Sleep* 21(7):759–767.
- Rodsutti J, Hensley M, Thakkinian A, D’Este C, Attia J. 2004. A clinical decision rule to prioritize polysomnography in patients with suspected sleep apnea. *Sleep* 27(4):694–699.
- Ross SD, Sheinait IA, Harrison KJ, Kvasz M, Connelly JE, Shea SA, Allen IE. 2000. Systematic review and meta-analysis of the literature regarding the diagnosis of sleep apnea. *Sleep* 23(4):519–532.
- Roth T, Drake C. 2004. Evolution of insomnia: Current status and future direction. *Sleep Medicine* (suppl 1):S23–S30.
- Ryan KL, Fedullo PF, Davis GB, Vasquez TE, Moser KM. 1988. Perfusion scan findings understate the severity of angiographic and hemodynamic compromise in chronic thromboembolic pulmonary hypertension. *Chest* 93(6):1180–1185.
- Sforza E, Johannes M, Claudio B. 2005. The PAM-RL ambulatory device for detection of periodic leg movements: A validation study. *Sleep Medicine* 6(5):407–413.
- Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Javier Nieto F, O’Connor GT, Boland LL, Schwartz JE, Samet JM. 2001. Sleep-disordered breathing and cardiovascular disease: Cross-sectional results of the Sleep Heart Health Study. *American Journal of Respiratory and Critical Care Medicine* 163(1):19–25.
- Sharafkhaneh A, Richardson P, Hirshkowitz M. 2004. Sleep apnea in a high risk population: A study of Veterans Health Administration beneficiaries. *Sleep Medicine* 5(4):345–350.
- Singh M, Drake C, Roehrs T, Koshorek G, Roth T. 2005. The prevalence of SOREMPs in the general population. *Sleep* 28(abstract suppl):A221.
- Sulit L, Storfer-Isser A, Kirchner HL, Redline S. 2006. Differences in polysomnography predictors for hypertension and impaired glucose tolerance. *Sleep* 29(6):777–783.
- Tachibana N, Ayas TA, White DP. 2005. A quantitative assessment of sleep laboratory activity in the United States. *Journal of Clinical Sleep Medicine* 1(1):23–26.
- Tice JA. 2005. *Portable Devices for Home Testing for Obstructive Sleep Apnea*. San Francisco: California Technology Assessment Forum.
- Trenkwalder C, Paulus W, Walters AS. 2005. The restless legs syndrome. *Lancet Neurology* 4(8):465–475.
- Westbrook PR, Levendowski DJ, Cvetinovic M, Zavora T, Velimirovic V, Henninger D, Nicholson D. 2005. Description and validation of the apnea risk evaluation system: A novel method to diagnose sleep apnea-hypopnea in the home. *Chest* 128(4):2166–2175.
- Whitney CW, Gottlieb DJ, Redline S, Norman RG, Dodge RR, Shahar E, Surovec S, Nieto FJ. 1998. Reliability of scoring respiratory disturbance indices and sleep staging. *Sleep* 21(7):749–757.
- Zou D, Grote L, Peker Y, Lindblad U, Hedner J. 2006. Validation a portable monitoring device for sleep apnea diagnosis in a population based cohort using synchronized home polysomnography. *Sleep* 29(3):367–374.

Opportunities to Improve Career Development in Somnology

CHAPTER SUMMARY *The science and prevalence of sleep loss and sleep disorders necessitates a larger and more interdisciplinary workforce to advance the field's knowledge base and provide optimal clinical care. In 2004, there were only 253 principal investigators working on 319 sleep-related research projects (NIH R01). Of the 253 principal investigators, only 151 researchers are involved primarily in clinical sleep research, and 126 focus primarily on basic research projects. Further, only 54 doctorates were awarded with a focus on somnology or sleep medicine. This workforce is insufficient, given the burden of sleep loss and sleep disorders. The National Institutes of Health (NIH) and private foundations have not adequately invested in increasing the research workforce. Since 1997, there have been no new requests for application or program announcements for sleep-related fellowship, training or career development programs. Further, over the period encompassing 2000 to 2004 there was a decrease in the number of career development awards. Given all this, the field is ripe for expansion, but there are too few young and midcareer investigators. To improve the pipeline of individuals in the field, it is critical that the NIH commit to increasing the number of fellowship, training, and especially career development awards. Further, given the limited number of individuals clustered at a small number of institutes, the NIH should fully embrace flexible mentoring programs that are capable of meeting the challenges.*

The relative paucity of individuals trained and committed to careers in sleep and sleep disorders research has been recognized by the National Center on Sleep Disorders Research (NCSDR). It identified the need to train investigators as the highest priority among the 10 major sections of their 2003 research plan (NHLBI, 2003). Attracting, training, and supporting investigators in sleep-related research is critical for fueling the scientific efforts needed to make important discoveries into the etiology, pathogenesis, prevention, and treatment of chronic sleep loss and sleep disorders. Further, it is also important to train individuals whose major role will be master clinician, organizer and manager of care, and clinician-educator. In 2004, there were only 151 researchers who had a clinical sleep-related research project grant (R01) and only 126 investigators focused primarily on basic sleep-related research projects.¹ The small number of research project grants, 331 in 2004, can be substantially attributed to the limited number of individuals working in the field. It is, therefore, of critical importance that further investment be made to expand the number of well-trained investigators in the field.

Many of the strategies described in Chapter 5 to increase the awareness among health care professionals will also likely attract new investigators into the field. These strategies include targeting the career interests of high school and college students, as well as graduate students and students in allied health fields. Further, as will be described in detail in this chapter, increasing the number of investigators in the field will require the National Institutes of Health (NIH), professional societies, patient advocacy groups, and others to significantly increase their investment in career development programs. As a result of the current limited pool of senior investigators and concurrent clustering of senior people at a limited number of academic centers, it will be equally important to adopt flexible mentoring programs that are capable of meeting the challenges.

GROWTH OF THE SOMNOLOGY AND SLEEP MEDICINE FIELD

Somnology and sleep disorders research is a relatively young discipline that has grown significantly over the last 35 years. However, the current workforce is still not adequate, given the public health burden of the disorders (Chapters 3 and 4). Since the establishment of the first sleep center in 1970, clinical recognition of sleep disorders has grown but is still not widely

¹Abstracts of all sleep-related R01s in the Computer Retrieval of Information on Scientific Projects (CRISP) database were analyzed under the following thesaurus terms: *insomnia, periodic limb movement disorder, restless legs syndrome, circadian rhythm, sudden infant death syndrome, sleep disorder, narcolepsy, sleep apnea, sleep, hibernation, and dream*. See Appendix A for further details.

acknowledged to be among the most common chronic health conditions (Chilcott and Shapiro, 1996; Young et al., 2002). Clinical advances have helped to attract and increase the number of clinicians and scientists to somnology and sleep medicine, as evidenced by the growth of membership in professional sleep societies. Since 1995, membership in the American Academy of Sleep Medicine (AASM) has more than doubled, while the Sleep Research Society (SRS) membership has almost tripled (Figure 7-1). However, the recent growth also emphasizes the need for a greater number of senior mentors and leaders in the field. The level of sleep-related research has grown, with over a 100 percent increase in the annual number of new NIH research project grants (R01) awarded in 1995 and 2004 (37 to 82). However, at the same time that the science and magnitude of the problem argues for greater investment, NIH funding of sleep-related activities has reached a plateau. Therefore, there are still substantial deficiencies in the workforce needed to address clinical somnopathy, and needs may be even greater relative to investment in research.

Growth in sleep-related research is limited by the paucity of funded investigators in the field. In 2004, only 253 investigators held active sleep-related NIH R01 grants. Although there has been an increase in the number of investigators since 1995, in comparison to other disorders, there are still too few sleep researchers. For instance, the absolute number of funded investigators with sleep-related projects is only around 80 percent of fields such as asthma,² which is a single disorder that affects 20 to 40 million. Further, funded investigators in sleep-related research tend to be older. The average age of all NIH investigators when awarded their first R01 has steadily risen and now is between 42 and 44 years of age (NIH, 2006b). However, in 2004, the average age of recipients at the time of their first R01 sleep-related grant was 51 (personal communication, M. Snyder, NIH Office of Scientific Affairs, November 8, 2005), which suggests an emergent need to replenish the pipeline with new investigators who can sustain the field and make it grow.

The limited number of researchers is clustered at a limited number of institutions. Of the 253 funded primary investigators in 2004, 33 percent of all investigators were at the top 10 academic sleep programs (ranking by the total number of somnology and/or sleep disorders grants), and 60 percent of all investigators were at the top 25 institutes (Appendix J). Likewise, 34 percent of all sleep-related R01 grants are awarded to the top 10 sleep

²314 individuals with asthma grants were identified by analyzing all 2004 R01 grants. Asthma grants were identified by all R01 grants that contained the word *asthma* as a thesaurus term. It is important to note that because only one search term was used, this search was not as thorough as the search performed for somnology and somnopathy R01 grants. Therefore, it may represent a significant under representation of the asthma field.

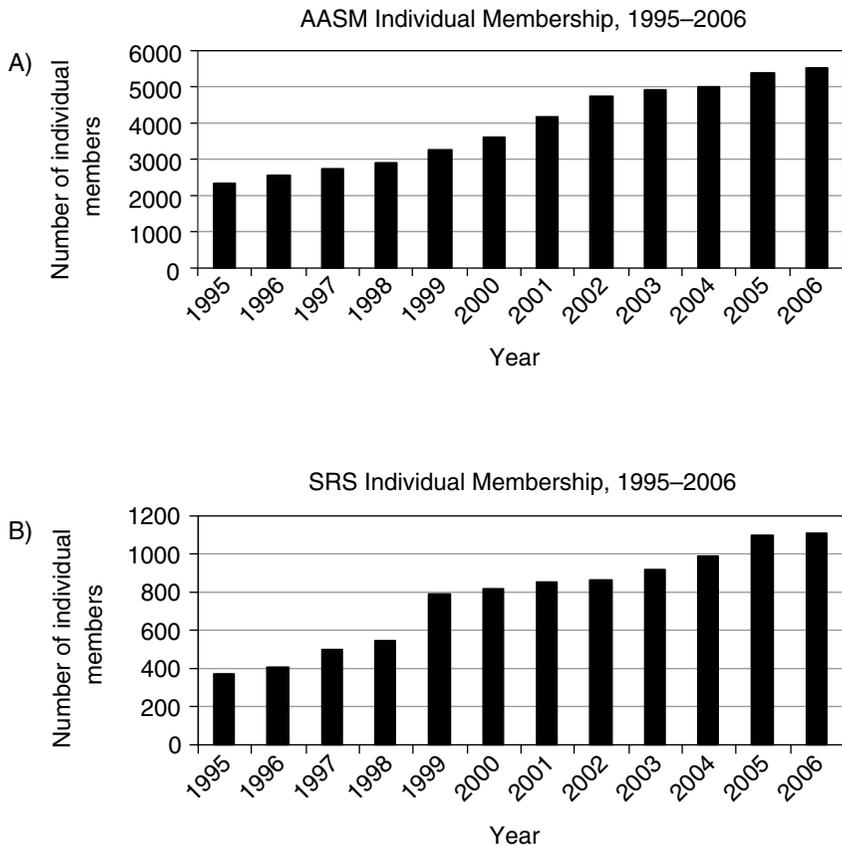


FIGURE 7-1 Individual membership in the AASM (A) and the SRS (B) has continued to grow over their history.

SOURCE: Personal communication, J. Barrett, AASM and SRS, (January, 2006).

academic programs, and 59 percent of all R01 grants are clustered in 25 institutions. In 2004, Harvard University, the University of Pennsylvania, and the University of Pittsburgh received 46 percent of sleep-related career development awards. Further, although many sleep disorders disproportionately affect minorities (Rosen et al., 2003), the number of minority investigators in the field is poorly representative (Spilsbury et al., 2004). In 2004, only 15 percent of all investigators with an R01 identified themselves as belonging to a minority ethnicity (Asian, African American, Hispanic, Pacific Islander, or other) (personal communication, M. Snyder, NIH Office of Scientific Affairs, November 8, 2005). As minority clinicians and investigators are more likely to work in underserved areas (Urbina et al., 1994), a

dearth of minority investigators may limit clinical research that requires access to minority populations and ultimately limit the translation of research advances to these important populations.

Barriers to Sleep Research Career Development

Barriers to attracting, training, and sustaining a critical mass of sleep investigators include the poor awareness among the general public and health care professionals and the availability of appropriate mentors to provide scientific and career guidance to new investigators.

Exciting basic science research and the dissemination of this excitement to a broad group of potential trainees are necessary and potentially rate-limiting steps in attracting new investigators from a limited pool of individuals committed to academic careers. In 2005, there were 204 student members of the SRS; only 54 individuals received a doctorate in sleep-related research, as compared to 158 in pain and 630 in cancer.³ Given the total number of principal investigators in the field, it appears that the majority of individuals with sleep-related doctorates do not remain in the field. Therefore, although there have been some remarkable successes in scientific investigation aimed at elucidating fundamental sleep physiology and biology (e.g., discovery of a mammalian *Clock* gene (Antoch et al., 1997; King et al., 1997; Tei et al., 1997) and the cause of narcolepsy (Lin et al., 1999; Chemelli et al., 1999; Mignot et al., 1999; Thannickal et al., 2000; Peyron et al., 2000), the future pace of scientific discovery is limited by the small numbers of active researchers pursuing basic investigation. Fundamental scientific discoveries play critical roles in galvanizing interest in any scientific discipline. Recruiting and retaining trainees in somnology and sleep medicine competes with other more established fields, many of which have made highly publicized advances, enjoy widespread respect across medical centers, and are more established as an academic discipline.

Investigators, particularly new ones who commit to interdisciplinary sleep-related research, are challenged to prove their value in academic medical centers that are accustomed to recognizing and rewarding individuals with “departmentally” defined research foci. Resource allocation needed to support new investigators may require complex negotiations among academic departments, which may deter new investigators or otherwise limit their access to needed support. In addition, identification of optimal mentoring relationships, critical for career development, will likely require sustained relationships among individuals with competing institutional commitments.

³Data were collected through a keyword search, using either *sleep*, *pain*, or *cancer*, of the Dissertation Abstracts database through DIALOG.

As for all scientific fields, new investigators require protected time and support as they transition to independent funding. Increasing fiscal pressures and, for physicians, demands to spend more time on clinical services, are threats to protected time critical for career development. New investigators are also often burdened with substantial debt from school loans, providing disincentives to participate in prolonged postdoctorate training.

NIH TRAINING AND CAREER DEVELOPMENT PROGRAMS

A variety of NIH-funded career development and academic training awards have been sponsored over the past decade (see Appendix H). In particular, there has been growth in the recognition and investment by the NIH in a broad variety of individual and institution-based career training programs, with a recent emphasis on clinical, translational, and interdisciplinary research training. Programs have been developed with the aims of attracting new trainees and developing the research and academic skills, and supporting their transition to independent and externally funded investigators (K01, K02, K08, K23, and K25). Other awards support midcareer development and mentorship skills (K24, K26). National Research Service Award Institutional Training Grants (T32) provide institutions with funds to support the training of individual postdoctoral candidates. The K30 and K12 series of NIH institutional training awards provide institutional support to develop new or expanded training programs and curriculum development.

NIH Support of Sleep-Related Training Activities

To determine the current investment in the field and how the grant portfolio has changed over the last 10 years, this committee performed a detailed review and analysis of the portfolio of NIH sleep-related awards in career training (K), fellowship (F), and training (T). Abstracts of all K, F, and T awards in the Computer Retrieval of Information on Scientific Projects (CRISP) database were analyzed. This database collects information on the number of federally funded biomedical research projects. Data from the CRISP database were used to assess the number of awards that were classified under the following thesaurus terms: *insomnia*, *periodic limb movement disorder*, *restless legs syndrome*, *circadian rhythm*, *sudden infant death syndrome*, *sleep disorder*, *narcolepsy*, *sleep apnea*, *sleep*, *hibernation*, and *dream*. To limit the number of grants that were not relevant to somnology or sleep disorders, the committee included only grants in which the key words appeared in both the thesaurus terms and the abstract and not the abstract alone. Temporal trends and distributions of awards across NIH institutes and to academic institutions were examined (see Appendixes H and J for compiled findings). The committee did not have access to the

applications that were submitted and not funded; therefore, it is not possible to conclusively determine if changes in investment are the result of NIH policy, the number and/or quality of submissions in each area, composition of grant review committees, or combination of these factors.

Temporal Analysis of Sleep Training Awards

Although there is a statistically significant increase in the total number of K awards from 1996 to 1998 (Appendix H), there was a relative leveling of total awards from 1998 to 2004—despite the establishment by the NIH of three new career development programs and significant increases in extramural funding. Further, since 1997, the NIH has not invested in a single sleep-related request for application (RFA) or program announcement (PA) career development program (Appendix F). Analysis of the number of sleep-related T and F awards shows an increase between 2000 and 2004 (Figure 7-2). However, the number of K awards decreased over the same time period and a larger proportion went to a smaller group of academic institutions. Three institutions, Harvard University, University of Pennsylvania, and University of Pittsburgh, accounted for 27 percent of all sleep-related T, K, and F grants received in 2000, 35 percent in 2004. This concentration is even greater if only K award distribution is analyzed. The same three institutions received 29 percent of all K awards in 2000, and 46 percent in 2004. This may reflect the extensive development of these programs and concentration of senior investigators.

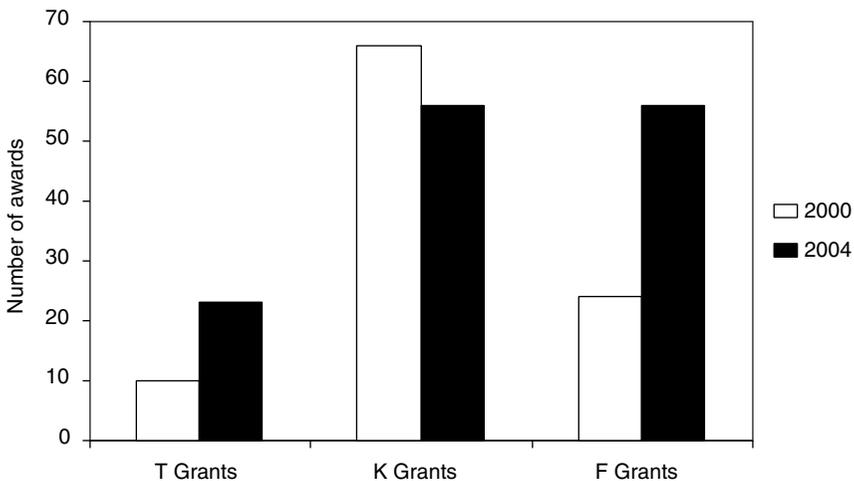


FIGURE 7-2 Total sleep training, career development, and fellowship grants in 2000 and 2004.

Support of training grants may also diminish. The NIH reported that in response to rising tuitions and steady budgets that if the current formula used to determine the number of awards is not altered there would be an overall loss of 4,000 training grant slots by 2015 (Bhattacharjee, 2005a).

Institute-Specific Funding of Career Development Awards

Career development awards in sleep are sponsored by numerous NIH institutes (see Appendix H). In general, for any given award category, with few exceptions no more than one new career development award was granted in any given year between 2000 and 2004. Since 2000, investment in career development awards for clinical scientists, K08 and K23, has varied. The National Institute of Mental Health (NIMH) and the National Heart, Lung, and Blood Institute (NHLBI) awarded the greatest number of grants. In 2003 and 2004 there was only one new K08 award. Although there has been greater investment in the K23 series, it is still minimal with five new awards in 2003 by four different institutes. K24 awards for mid-career development have also been minimal in 2003 and 2004, with no new awards in 2003 and only three in 2004—two of which were by the NHLBI.

There has also been very limited investment in the K07 academic career awards, designed to improve curricula and emphasize development of scientist leadership skills. Apart from the Sleep Academic Award program, there has been very little investment through the K07 mechanism, no new awards were granted in 2003, and only three in 2004. Further, no institute apart from the NHLBI has supported this mechanism for sleep-related awards.

Over the 5-year period between 2000 and 2004, there has been even less investment in career development awards for mentored research (K01), independent scientists (K02), and senior scientists (K05). All three of these mechanisms historically have been used to support basic research. NIMH was the first institute that supported these three mechanisms for sleep-related activities, but in recent years there has been a marked decrease. For example, in 2002, the NIMH supported six sleep-related K01 awards, seven K02 awards, and two K05 awards. In 2004, these numbers have decreased to two K01 awards, two K02 awards, and one K05 award. These latter statistics underscore the relatively small amount of investment of any given institute in sleep research training, with no evidence that any institute or the Trans-NIH Sleep Research Coordinating Committee has assumed leadership in this area. Although the decrease in career development awards is dramatic, it is important to note that over the same period, there has been an increase in fellowship awards (Appendix I).

Of the 314 career development awards that were funded during the five years between 2000 and 2004, NHLBI sponsored 94 (29 percent), and the NIMH sponsored 162 (52 percent). One third (32 of the 94) of sleep-related

NHLBI-sponsored training grants were K07 awards devoted to the Sleep Academic Award program, which were designed to support the development of curricula and educational leadership, not research training. The vast majority of the Trans-NIH Sleep Research Coordinating Committee member institutes—many of whom have a large portion of the sleep-related research project grant portfolio (Appendix G)—have minimally supported career development. The underlying reasons may be multiple, including poor or low numbers of applications, insufficient sleep-related research expertise on study sections (which is also partially affected by a limited number of senior members of the field), and lack of awareness of the extent of the problem. Further, K awards are expensive; consequently, institutes are often reluctant to invest heavily in the K awards, especially in periods of budget constraints.

One potential strategy to offset the lack of investment would be to leverage the combined resources from multiple member institutes of the Trans-NIH Sleep Research Coordinating Committee to develop a larger pool of money for training programs. In 2003, the NIH supported 845 K23 career development awards at a total cost of over \$114 million, or an average annual cost of \$135,000 per award. If four institutes were to cosponsor a K23 program in somnology or sleep medicine, this would cost each institute approximately \$34,000 annually per award, a 75 percent decrease in expense. The committee strongly recommends joint investment in training programs; it does so recognizing that there are potentially increased overhead costs associated with tracking and implementing an annual transfer of funds between institutes. Further, mechanisms need to be developed to enable all institutes contributing to a joint effort to be acknowledged in congressional goals for new grants.

NIH Roadmap Initiatives

As part of the NIH director's research agenda, a series of roadmap initiatives was identified to foster the development of interdisciplinary training for investigators at all levels of their careers. These initiatives emphasize translational research, behavioral/social sciences, and quantitative sciences. Between 2004 and 2005, \$8 million was invested in the establishment of seven K12 Multidisciplinary Clinical Research Training Programs (NIH, 2006a). Because sleep-related research is particularly well suited to interdisciplinary and translational strategies, it could serve as one of several key programs for these new initiatives

New NIH Career Award Support

Recognizing the difficulty of becoming an independent researcher and in response to the Institute of Medicine's and National Academies' report,

Facilitating Interdisciplinary Research, on fostering independence among young biomedical researchers, the NIH recently announced the creation of three new initiatives (Bhattacharjee, 2005b). Each initiative is designed to facilitate postdoctoral fellows into independent faculty positions. The first—the NIH Pathway to Independence Award program—is a 5-year award composed of two phases (NIH, 2006b). The initial phase (K99) is a 1- to 2-year mentored period designed to allow investigators to complete their supervised research work, publish results, and search for an independent faculty position. The second, independent phase (R00) would comprise the remaining 3 years of the award and is structured to provide financial support to awardees who secure an assistant professorship while they establish their own research program and successfully apply for an NIH investigator-initiated (R01) grant. The second mechanism is an independent research grant program, which does not require preliminary data. The final initiative is to speed up the R01 grant application turnaround time for new researchers who fail to receive an award on their first attempt.

Summary of NIH Support of Career Development Programs

In summary, analysis shows that no single NIH institute has made substantive investments into sleep-related research career development or training awards. There are alarming downward temporal trends in level of support for research training and career development, suggested by the recent drop in funded K awards, with further clustering of funding to fewer institutions. Institutes that support large levels of sleep research funding should also be encouraged to make a significant investment in career development initiatives. Funding trends also suggest that there are very few individuals with training support to develop careers in basic sleep science. There are many existing training grants or large research programs in disciplines related to somnology or sleep medicine (e.g., internal medicine, neurology, psychiatry, psychology, otolaryngology, nursing, epidemiology, neuroscience, and health services research). Given the interdisciplinary nature of the field, these programs provide an additional mechanism for increasing the number of somnology and sleep medicine trainees. Although there is an exciting national movement toward supporting interdisciplinary and translational research highlighted in roadmap initiatives, existing programs largely have not recognized the potential of the somnology and sleep medicine field as a prototype for these initiatives. This represents a great opportunity to both foster development of sleep research and to forge new interdisciplinary approaches.

Professional Organization and Foundation Support of Career Development

Professional societies have played important roles in sponsoring career development across a wide variety of disciplines. Well-established career training awards are available from professional organizations with interest in somnology and sleep disorders, such as the American Heart Association, American Diabetes Association, American College of Chest Physicians, American Lung Association, and the American Thoracic Society, among others. Table 7-1 shows the number of career development awards several organizations made in 2004. Since sleep-related research is relevant to several of these organizations, the number of sleep-related training grants is also provided. It is worth noting that investment in sleep-related research is low for all professional organizations profiled below; for example, despite the significant association of sleep disorders and cardiovascular disease, only 2 of the 845 awards given by the American Heart Association's career training program portfolio supported sleep-related research. One impediment leading to the limited support from these organizations is that they might not recognize the important role they have in fostering interdisciplinary research, as they are focused on more traditional organ-based research.

There are two primarily sleep-focused organizations that have training awards: the National Sleep Foundation (NSF)'s Pickwick Club Award, and the American Sleep Medicine Foundation (ASMF)'s Faculty Career Advancement Award.

The ASMF, affiliated with the American Academy of Sleep Medicine, annually sponsors between four and six fellowship awards, each as much as 2 years in duration and for a maximum annual funding level of \$60,000. From 2003 to 2005 the program received on average 18 applications (personal communication, R. Money, AASM, November 9, 2005). In 2005, the

TABLE 7-1 Career Training Awards by Professional Organizations with Secondary Interests in Sleep (2004)

	Total Awards	Sleep Awards
American Heart Association	845	2
American Diabetes Association	9	0
American College of Chest Physicians	11	1
American Lung Association	115	2
American Thoracic Society	6	0

NOTE: The information contained in this table was obtained from personal communication with appropriate staff members at each organization.

ASMF also developed the AASM/Pfizer Scholars Grant Program in Sleep Medicine to provide support for career development of junior faculty in somnology and sleep medicine.

The Pickwick Club Fellowship of the NSF, an independent public health advocacy organization, awards two to four fellowships of 1 to 2 years in duration for postdoctorate trainees in sleep-related research. Support is primarily for annual salary support (\$35,568 to \$45,048). In 2004, investment in research training by the NSF is estimated at approximately \$180,000.

Foundations, such as the Francis Family Foundation, have made notable contributions to training pulmonary scientists through the Parker B. Francis Fellowship Program. Over the last 30 years, this foundation has contributed nearly \$40 million in support of more than 600 fellows, some of whom have worked in the somnology and sleep medicine field. Each award is for 3 years, and provides stipends, fringe benefits, and travel expenses to postdoctoral fellows or newly appointed assistant professors to enable their research development related to pulmonary disease and lung biology. A survey of former fellows demonstrated that greater than 90 percent of respondents are currently employed in academic settings and spend a significant portion of their time on research.

Summary of Foundation Support of Career Development Programs

Given the overall paucity of support, further investment is required by private foundations for career development. Foundations, such as the Parker B. Francis Foundation and the Cystic Fibrosis Foundation (Box 7-1) are excellent models of sustained foundation support for research career development. Although professional organizations cannot directly support research fellowships, through associated foundations they have made moderate to large investments in research career development, including funding for some trainees with a primary somnology and somnopathy focus. Funds for these programs have been derived from endowments and well-organized, targeted fund-raising efforts. This analysis identifies the potential availability of funding for sleep training from multi- and interdisciplinary initiatives available through professional organizations with secondary interests related to sleep loss and/or sleep disorders, in addition to the need for organizations with primary sleep-related agendas to invest more heavily in developing the next generations of investigators. Similar to the committee's call for multiple institutes of the Trans-NIH Sleep Research Coordinating Committee to combine resources to support career development programs, private foundations should also explore mechanisms to coordinate their efforts. This will ensure that the maximal effect from these efforts is realized.

BOX 7-1
Model Investment by a Foundation into
Career Development: The Cystic Fibrosis Foundation

An example of a scientific community that has rallied to support the career development of research trainees is in cystic fibrosis. Despite the relative rarity of this condition in the population (30,000 children and adults), and the relatively small pool of researchers available to recruit from, foundation support has succeeded in developing a cadre of productive researchers, who largely have a strong history of sustained academic contributions. Three key programs have been developed through the Cystic Fibrosis Foundation: the Clinical Fellowship Program, the LeRoy Mathews Program, and the Harry Shwachman Fellowship. Together, these programs provide support for the full spectrum of trainees: combined clinical/research fellowship training, early research career development (enrolling fellows within the first 4 years of training), and junior faculty development. Support for these programs is derived from well-organized fund-raising and philanthropy. The combined support for these training programs represents approximately 2 percent of the annual Cystic Fibrosis Foundation budget.

The Clinical Fellowship Programs expose fellows early in their training to working in a multidisciplinary team environment. Annually, approximately 23 fellows are supported, at a total cost of \$1.2 million. It supports first and second years for the clinic, and during the third and fourth year supports time for basic, translational, or clinical research. Fellows receive an annual base salary of \$52,000 with an additional \$10,000 for research supplies. Most junior and many senior faculty members who staff the 115 accredited Cystic Fibrosis Foundation centers have derived some support through this program.

The LeRoy Mathews program is a smaller program, with an annual cost of approximately \$345,000. It targets the development of fellows and their transition to a junior faculty role. Each awardee is supported for 6 years. Two fellows are supported at any given time. Fellows may be accepted into the program up to their fourth year of specialty training.

The Harry Shwachman fellowships are 3-year programs that target junior faculty with the goal of supporting their development as independent investigators. These awards are considered to be equivalent to NIH K08 awards in the scope of support for protected time and in the requirement for mentored research.

The Cystic Fibrosis Foundation also utilizes these programs to create a “community” of scholars through sponsorship of fellows to attend special sessions at national meetings.

The Role of Mentoring and Availability of Sleep Mentors

Numerous studies have documented the pivotal role of mentoring in career development (Chilcott and Shapiro, 1996; Palepu et al., 1998; Young et al., 2002; Lieff et al., 2003). The Council of Graduate Schools promoted the concept that: "Mentors are advisors, people with career experience willing to share their knowledge; supporters, people who give emotional and moral encouragement; tutors, people who give specific feedback on one's performance; masters, in the sense of employers to whom one is apprenticed; sponsors, sources of information about and aid in obtaining opportunities; models of the kind of person one should be to be an academic" (Zelditch, 1995). The cornerstone of most training programs, including NIH and foundation-funded programs, is evidence of a strong mentor-mentee relationship. Multiple mentors are required for multidisciplinary research training. Many advocate for formal oversight committees for trainees and junior faculty. Successful peer-reviewed training awards include clearly articulated roles for mentors as the responsible agents for overseeing the entire scope of the trainee's career development program.

The availability of appropriate mentors to provide scientific and career guidance to new investigators (as well as to serve as a catalyst to attract such individuals to the field) is limited, with some variation across institutions. There is currently a concentration of investigators and grants at a limited number of academic institutions. Even highly established sleep academic centers have a paucity of senior mentors. This often requires senior mentors to be responsible for several mentees, potentially reducing the effectiveness of the mentorship relationship. The availability of mentors is also limited by the fiscal constraints of academic medical systems and structures, which normally do not always recognize the contribution of mentoring to the institute's mission. Increasing fiscal pressures at academic centers require faculty to be increasingly accountable for justifying their effort in relationship to compensation. Mentoring is, in general, not a compensated activity. Thus, there are growing disincentives for potential mentors to assume new mentorship relationships.

The limited availability of appropriate mentors has far-reaching consequences to the growth of the field. Trainees may make decisions to enter certain fields because of the reputation of accessible mentors. Securing protected time and research support from external sources requires commitment by at least one strong mentor. Young investigators benefit enormously by relationships with a mentor who can help negotiate complex academic settings, prioritize goals and work, critically examine research methods and data interpretation, refine presentation and scientific and grant-writing skills, and develop high levels of professionalism.

OPPORTUNITIES TO ACCELERATE SOMNOLOGY AND SLEEP MEDICINE CAREER DEVELOPMENT

Each challenge also presents opportunities to develop novel strategies for career development, to enhance the recognition of somnology and sleep disorders research as an interdisciplinary field and more effectively interface with other related disciplines, and to build upon existing NIH and private foundation initiatives. In addition to strategies described in Chapter 5, additional strategies include the following:

- Training in somnology and sleep medicine can be structured to complement those of other programs and vice versa, by interactively engaging trainees in other programs. The interdisciplinary organization of the field creates a foundation for trainees from multiple fields to participate and apply their methods or expand their initial foci to questions relevant to somnology and somnopathy. The NIH can foster this by adopting trans-institutional training programs.

- The NIH Roadmap explicitly emphasizes the importance of interdisciplinary research, especially aimed at achieving translational research objectives. As academic institutions vie for support from NIH Roadmap programs, incorporation of somnology and sleep disorders research as a translational research focus may provide a competitive edge.

- The innovation of the new NIH K12 training programs—which provide support to an educational institution for career development experiences for clinicians leading to research independence—and their sensitivity to respond to the scientific needs of the community make these programs desirable avenues for providing support for both mentors and mentees interested in somnology and sleep disorders. Modern communication technologies make long-distance mentoring feasible and effective.

- Recent loan repayment policies have been initiated at the NIH, which may substantially reduce the burden of loan repayment in return for evidence of scientific activity and further investment in academic training. Targeting sleep-related research trainees and junior faculty for NIH loan repayment is suggested as a potentially important recruitment tool. Availability of NIH and foundation training programs are a crucial source of support to ensure protected time and resource investment in new investigators.

- The growing strength of several private organizations (e.g., foundations, professional societies, industry) committed to promoting sleep health and somnology and sleep disorders professionals is a largely untapped resource for support for trainees.

Potential Mechanisms to Improve Training

A particular challenge for development of investigators in sleep research is that currently few institutions have the critical mass of established investigators in this area to provide mentorship and training. This suggests that mechanisms need to be sought to leverage the intellectual resources at these few institutions.

Remote Mentoring Programs

Successful career development awards require the identification of a strong mentor. However, if such mentors may only be located at the candidate's home institution, there would be little growth of somnology and/or sleep disorders research expertise in institutions other than the few large academic programs. Further, educating grant reviewers of career development applications allows more flexibility in the range of mentorship relationships—a flexibility needed to allow the field to grow.

There are several NIH mechanisms to support midcareer development and mentorship skills (K24, K25). In 2004, however, only three individuals were awarded a new K24 grant in somnology and/or sleep medicine (no new grants were awarded in 2003), and there were no new K25 awards in somnology and/or sleep medicine for the same year. The new K12 Translational Research Institutional Training program also provides salary support for mentees. However, no K12 scholars identified a sleep-related focus in their research application. These data indicate the need for greater NIH investment in developing and supporting the effort of mid- to senior-level investigators as mentors and to provide support for mentoring time.

Specialized NIH programs have also been developed to facilitate the creation of national networks of mentors and mentees. However, due to budgetary constraints, some NIH institutes are no longer funding undergraduate programs. Two programs were very successful in developing mentoring skills of mentors, creating new mentor-mentee relationships, and exposing trainees to intensive research experiences—Brown University's Summer Sleep and Chronobiology Research Apprenticeship (see Chapter 5) and the Summer Research Institute in Geriatric Psychiatry (Box 7-2) (Halpain et al., 2001).

Another approach to efficiently “matching” mentors and mentees across institutions is through networks supported by professional societies. The American Thoracic Society established a mentoring program in 1999 and serves as a clearinghouse for mentors and mentees with complementary issues (and sometimes concordant gender). The American Thoracic Society provided venues for matched mentors and mentees to meet with the goal of facilitating the mentoring relationship.

BOX 7-2
Summer Research Institute:
A Model Program for Mentor-Mentee Networks

The Summer Research Institute is a 10-year-old program that has created a national network of mentors in a relatively small field (geriatric psychiatry). The Summer Research Institute provides a useful model for attracting new investigators to a defined field and for bridging and shortening the transition period from fellowship to first research funding. The program offers a 1-week “boot camp” in research career survival skills for postdoctorates and junior faculty. At the end of each program, a workshop facilitates interactions and sharing of research among all trainees. The program’s success is evidenced by the career trajectories of trainees. Of the approximately 300 program alumni (postdocs, junior faculty), 80 percent now hold full-time academic positions, and 50 percent or so have competed successfully for extramural research from the NIH and foundations.

In 2005, the SRS and the AASM also initiated a long-distance mentor-mentee program. This program is still under development; too few data are available to evaluate its effectiveness or level of participation.

In summary, the pivotal role of mentorship in attracting trainees to sleep medicine and facilitating their academic success is clear. Given the relatively small numbers of available mentors, additional efforts are needed to encourage NIH, professional societies, and foundations to provide support for developing mentors. In addition, creative use of national networks of mentors and mentees needs to be encouraged. Funding agencies need to recognize the role of long-distance mentorship plans, if those plans adequately address important issues in successful mentor-mentee relationships.

Given all this, the field is ripe for expansion, but there are too few young and midcareer investigators.

*Integration of Somnology and Sleep Medicine with
Other Training Programs*

Another strategy to be considered is providing additional training positions to already established training grants in relevant disciplines, such as neuroscience and clinical epidemiology. This, when combined with the remote mentorship model, would have considerable benefit. It would not only provide a new mechanism to provide training to trainees, but also the men-

tor with expertise in the primary discipline, such as neuroscience or clinical epidemiology, at the host institution might also become interested in sleep research.

The development of midcareer mentoring awards for 1 to 2 years would allow midcareer investigators in institutions with little sleep expertise but relevant skills (e.g., neuroscience or clinical epidemiology) to get retrained in sleep research. They would do so in collaboration with one of the comprehensive sleep centers described elsewhere in this report. Such mentoring could be a combination of time spent at the comprehensive sleep center and remote mentorship while at their own institution. The home institution would need to indicate its commitment to developing a sleep research program for this to be a viable, productive strategy.

Somnology—the branch of science devoted to the study of sleep and wakefulness—requires a larger interdisciplinary research workforce. This can be accomplished by both attracting individuals from other related fields and by establishing a new cohort of researchers who work specifically on sleep-related topics. As presented in this chapter, the current status of the sleep research field requires new mechanisms to be considered to seed institutions that currently lack the intellectual resources.

Recommendation 7.1: The National Institutes of Health and private foundations should increase investment in interdisciplinary somnology and sleep medicine research training and mentoring activities.

The National Institutes of Health, foundations, and professional societies should utilize and develop further funding mechanisms to attract young investigators into the field of somnology and sleep medicine. As a reflection of the interdisciplinary nature of somnology and sleep medicine, members of the Trans-NIH Sleep Research Coordinating Committee should be encouraged to combine resources to sponsor grants for disciplinary and cross-disciplinary training and mentoring activities (T, F, and K funding mechanisms) of medical students, graduate students, postdoctoral fellows, clinical fellows, and junior faculty.

To implement this recommendation the following should be considered:

- The Trans-NIH Sleep Research Coordinating Committee should establish a somnology and sleep medicine career development program. This program should support trainees for a significant number of years, spanning research training in fellowship and research career development as a faculty member. It should also

facilitate mid-career training opportunities (e.g., K21, K24), the Academic Career Award for Education and Curriculum Development program (K07), and research education grants (R25).

- Existing training grants or large research programs in disciplines related to somnology or sleep medicine (e.g., internal medicine, neurology, psychiatry, psychology, otolaryngology, nursing, epidemiology, neuroscience, health services research) should allow for the addition of a sleep medicine trainee. Where pertinent expertise is not available on-site, remote mentoring at other institutions should be encouraged.

REFERENCES

- Antoch MP, Song EJ, Chang AM, Vitaterna MH, Zhao Y, Wilsbacher LD, Sangoram AM, King DP, Pinto LH, Takahashi JS. 1997. Functional identification of the mouse circadian *Clock* gene by transgenic BAC rescue. *Cell* 89(4):655–667.
- Bhattacharjee Y. 2005a. NIH career awards. Universities may have to pay more in support of graduate training. *Science* 310(5754):1601.
- Bhattacharjee Y. 2005b. NIH career awards. Young scientists get a helping hand. *Science* 310(5754):1601.
- Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammell T, Lee C, Richardson JA, Williams SC, Xiong Y, Kisanuki Y, Fitch TE, Nakazato M, Hammer RE, Saper CB, Yanagisawa M. 1999. Narcolepsy in orexin knockout mice: Molecular genetics of sleep regulation. *Cell* 98(4):437–451.
- Chilcott LA, Shapiro CM. 1996. The socioeconomic impact of insomnia. An overview. *Pharmacoeconomics* 10(suppl 1):1–14.
- Halpain MC, Jeste DV, Katz IR, Reynolds CF. 2001. Summer Research Institute: Enhancing research career development in geriatric psychiatry. *Academy of Psychiatry* 25: 48–56.
- King DP, Zhao Y, Sangoram AM, Wilsbacher LD, Tanaka M, Antoch MP, Steeves TD, Vitaterna MH, Kornhauser JM, Lowrey PL, Turek FW, Takahashi JS. 1997. Positional cloning of the mouse circadian *Clock* gene. *Cell* 89(4):641–653.
- Lieff SJ, Tolomiczenko GS, Dunn LB. 2003. Effect of training and other influences on the development of career interest in geriatric psychiatry. *American Journal of Geriatric Psychiatry* 11(3):300–308.
- Lin L, Faraco J, Li R, Kadotani H, Rogers W, Lin X, Qiu X, de Jong PJ, Nishino S, Mignot E. 1999. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. *Cell* 98(3):365–376.
- Mignot E, Young T, Lin L, Finn L. 1999. Nocturnal sleep and daytime sleepiness in normal subjects with HLA-DQB1*0602. *Sleep* 22(3):347–352.
- NHLBI (National Heart, Lung, and Blood Institute). 2003. *National Sleep Disorders Research Plan, 2003*. Bethesda, MD: National Institutes of Health.
- NIH (National Institutes of Health). 2006a. *Roadmap Initiative to Provide Training for Future Leaders of Clinical Research*. [Online]. Available: <http://nihroadmap.nih.gov/clinicalresearch/clinicaltraining/futureleaders.asp> [accessed January 25, 2006].
- NIH. 2006b. *Resources for New Investigators*. [Online]. Available: http://grants2.nih.gov/grants/new_investigators/ [accessed January 25, 2006].

- Palepu A, Friedman RH, Barnett RC, Carr PL, Ash AS, Szalacha L, Moskowitz MA. 1998. Junior faculty members' mentoring relationships and their professional development in U.S. medical schools. *Academy of Medicine* 73(3):318-323.
- Peyron C, Faraco J, Rogers W, Ripley B, Overeem S. 2000. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nature Medicine* 6(9):991-997.
- Rosen CL, Larkin EK, Kirchner HL, Emancipator JL, Bivins SF, Surovec SA, Martin RJ, Redline S. 2003. Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: Association with race and prematurity. *Journal of Pediatrics* 142(4):383-389.
- Spilsbury JC, Storfer-Isser A, Drotar D, Rosen CL, Kirchner LH, Benham H, Redline S. 2004. Sleep behavior in an urban U.S. sample of school-aged children. *Archives of Pediatrics and Adolescent Medicine* 158(10):988-994.
- Tei H, Okamura H, Shigeyoshi Y, Fukuhara C, Ozawa R, Hirose M, Sakaki Y. 1997. Circadian oscillation of a mammalian homologue of the *Drosophila* period gene. *Nature* 389(6650):512-516.
- Thannickal TC, Moore RY, Nienhuis R, Ramanathan L, Gulyani S, Aldrich M, Cornford M, Siegel JM. 2000. Reduced number of hypocretin neurons in human narcolepsy. *Neuron* 27(3):469-474.
- Urbina C, Hickey M, McHarney-Brown C, Duban S, Kaufman A. 1994. Innovative generalist programs: Academic health care centers respond to the shortage of generalist physicians. *Journal of General Internal Medicine* 9(4 suppl 1):S81-S89.
- Young T, Peppard PE, Gottlieb DJ. 2002. Epidemiology of obstructive sleep apnea: A population health perspective. *American Journal of Respiratory and Critical Care Medicine* 165(9):1217-1239.
- Zelditch M. 1995. *A Conversation About Mentoring: Trends and Models*. Washington, DC: Council of Graduate Medical Schools.

8

Bolstering Somnology and Sleep Disorders Research Programs

CHAPTER SUMMARY *The National Center on Sleep Disorders Research (NCSDR) and the Trans-NIH Sleep Research Coordinating Committee were established to coordinate the sleep-related research, training, and education activities at the National Institutes of Health (NIH). At the same time that the science and magnitude of the public health and economic burden requires greater investment, the output from the NCSDR and Trans-NIH Sleep Research Coordinating Committee has not kept pace. As a consequence, NIH funding for sleep-related activities has reached a plateau, and the future outlook for somnology and sleep medicine is unclear. A detailed examination of the past and current investment in sleep-related research demonstrates that there are only 331 funded research projects and 253 independent investigators, far below the requirements of the field. Further, of the 253 principal investigators only 151 researchers are primarily involved in clinical sleep research and 126 primarily focus on basic research projects. The challenge for the field is to develop a collaborative and focused approach with a strong research infrastructure. To bolster clinical and basic research efforts, catalyze collaborative research efforts, and attract the breadth of talented researchers who will be able to move somnology and sleep disorders research and clinical care forward to achieve optimal outcomes requires a coordinated and integrated strategy. The NCSDR, its advisory board, and the Trans-NIH Sleep Research Coordinating Committee need to take a proactive role in providing continued leadership. Further, a research network is of particular importance in the*

field because of the need for a coordinated interdisciplinary research approach to basic and clinical research, clinical care, public education, and training. Therefore, the NIH should establish Somnology and Sleep Medicine Centers of Excellence within a National Somnology and Sleep Medicine Research and Clinical Network.

The field of somnology and sleep medicine is poised to take great strides in elucidating and addressing the etiology, pathogenesis, and public health burden of chronic sleep loss and sleep disorders. This strong position is the result of the National Institutes of Health (NIH) establishing the Trans-NIH Sleep Research Coordinating Committee and the National Center on Sleep Disorders Research (NCSDR). However, at the same time that the science and magnitude of the problem requires greater investment, NIH funding to sleep-related activities has reached a plateau. Consequently, the future outlook for somnology and sleep medicine is unclear. The next significant advances necessitate leveraging these resources to their utmost potential in conducting research and refining diagnosis and treatment interventions for sleep loss and sleep disorders.

This chapter provides an overview of the current coordination of sleep-related activities at the NIH, including an evaluation of the NCSDR. Included in the evaluation is a detailed summary of sleep-related research activities sponsored by the NIH between 1995 and 2004. The chapter culminates with a discussion on the next steps required to accelerate progress, including the establishment of a National Somnology and Sleep Medicine Research and Clinical Network.

NIH COORDINATION OF SLEEP-RELATED ACTIVITIES

To a greater extent than many medical and research disciplines, the field of somnology and sleep medicine cuts across many disciplines, including but not limited to cardiology, dentistry, endocrinology, epidemiology, geriatrics, molecular biology, neurology, neurosciences, nursing, nutrition, otolaryngology, pediatrics, pharmacology, psychiatry, and pulmonology. In 2004, there were 331 sleep-related research project grants sponsored by 17 institutes at the NIH (Table 8-1, Appendix G). The NIH has two mechanisms to coordinate its sleep-related activities, the Trans-NIH Sleep Research Coordinating Committee and the NCSDR.

TABLE 8-1 NIH Institute Support of Somnology and Sleep Disorders Research Project Grants (R01) in 2004

Institute	Number of Grants
National Heart, Lung, and Blood Institute	102
National Institute of Mental Health	88
National Institute of Neurological Disorders and Stroke	49
National Institute on Aging	31
National Institute of General Medical Sciences	22
National Institute of Nursing Research	19
National Eye Institute	15
National Institute on Drug Abuse	13
National Institute on Alcohol Abuse and Alcoholism	12
National Institute of Diabetes and Digestive and Kidney Diseases	11
National Institute of Child Health and Human Development	10
National Cancer Institute	7
National Institute of Arthritis and Musculoskeletal and Skin Diseases	5
National Institute on Deafness and Other Communication Disorders	4
National Center for Complementary and Alternative Medicine	3
National Institute of Allergy and Infectious Diseases	1
Fogarty International Center	1

NOTE: Institutes and centers in bold are not members of the Trans-NIH Sleep Research Coordinating Committee.

Trans-NIH Sleep Research Coordinating Committee

In 1986, the Director of the NIH established the Trans-NIH Sleep Research Coordinating Committee to facilitate an interchange of information about somnology and sleep disorders research. This coordinating committee meets every 2 to 3 months to discuss current sleep-related activities within the NIH and develop new programs. Currently 13 NIH institutes and offices are members of the Trans-NIH Sleep Research Coordinating Committee. The director of the NCSDR chairs the Coordinating Committee, and its members are program staff from the various NIH institutes with an interest in somnology and sleep disorders. Although most institutes that support sleep-related research are members of the coordinating committee, a few are not (Table 8-1), including the National Institute of General Medical Sciences and the National Eye Institute. In 2004 these two institutes each supported more sleep-related grants than 8 of the 13 current members—close to 10 percent of all sleep-related research project grants.

The Trans-NIH Sleep Research Coordinating Committee offers the somnology and sleep medicine field an exceptional resource for increasing and coordinating NIH support of interdisciplinary sleep-related research

and career development programs. Over the last 10 years, through requests for applications (RFAs) and program announcements (PAs), members of the coordinating committee have cosponsored 16 out of the 18 research project grant initiatives (Appendix F). This has the advantage of spreading out the costs of an initiative over multiple institutes, thus being able to support greater investment. However, as will be discussed in greater detail later in this chapter, recently the coordinating committee has not taken a proactive role in developing new research programs.

National Center on Sleep Disorders Research

In direct response to the 1993 report of the National Commission on Sleep Disorders Research, *Wake Up America: A National Sleep Alert*, a provision of the NIH Revitalization Act instructed the Director of the NIH and the National Heart, Lung, and Blood Institute (NHLBI) to establish the NCSDR. As described in the congressional language, the mission of the NCSDR is to “conduct and support of biomedical and related research and research training, the dissemination of health information, and the conduct of other programs with respect to various sleep disorders, the basic understanding of sleep, biological and circadian rhythm research, chronobiology and other sleep related research” (U.S. Congress, Senate, 1993). As mandated by Congress the NCSDR has the authority:

- for the conduct and support of research, training, health information dissemination, and other activities with respect to sleep disorders, including biological and circadian rhythm research, basic understanding of sleep, chronobiological and other sleep-related research; and
- to coordinate the activities of the NCSDR with similar activities of other federal agencies, including the other agencies of the NIH, and similar activities of other public entities and nonprofit entities. (See Appendix D for complete congressional language.)

The NCSDR establishment within the NHLBI allowed it to call upon the existing successful programs at the NHLBI in sleep-disordered breathing as well as the NHLBI's expertise in public education programs. It was realized at the inception of the NCSDR that there was a major need to educate both public and health care professionals about sleep and sleep disorders. Because many NIH institutes have a strong interest in somnology and sleep disorders research and fund portfolios of grants in this area, it was not envisioned that all funding for sleep-related programs would be done through the NCSDR. Rather, the NCSDR would facilitate development of research and training programs in areas of identified need. In addition, it would be a center that facilitated and coordinated research across

the many institutes of the NIH with an interest in sleep-related research, as well as across the many federal agencies that have an interest in sleep deprivation and sleep disorders. These agencies include: the Centers for Disease Control and Prevention (CDC) (prevalence and impact of sleep disorders, inadequate sleep); the Department of Defense (impact of sleep deprivation and nighttime activity on human performance); the Department of Transportation (crashes occurring from falling asleep at the wheel); the Occupational Safety and Health Administration (impact of sleep deprivation and sleep disorders on industrial accidents and shift work sleep disorder); and the Department of Veterans Affairs (VA) (impact of sleep disorders on health of veterans, posttraumatic stress disorder). It is of note that although one out of every five Americans perform shift work, the Department of Labor withdrew its membership from the NCS DR advisory board in 2003. Following the departure of the department's representative the Department of Labor chose not to appoint a replacement member. The committee hopes that the Department of Labor will reconsider this, as it can make an important contribution to the national effort to decrease the burden of sleep loss and sleep disorders.

Several federal agencies have research and public education programs including the Department of Defense, the Department of Transportation, and the CDC. However, the NCS DR has not made clear or demonstrated far-reaching coordination of these activities, with potential missed opportunities for integrating sleep-related programs among federal agencies and departments. The original mandate to the NCS DR, as envisioned in the authorizing legislation, saw the CDC playing a major role in public education and surveillance. As described in Chapter 5, the CDC is involved in many public education campaigns and national surveys. Apart from the recent addition of sleep-related questions in the National Health and Nutrition Examination Survey (NHANES), this has not occurred. There are insufficient data about the sleep patterns of Americans, and the CDC's expertise should be sought in conducting surveillance, monitoring sleep disorders and sleep habits, and developing public health campaigns about sleep loss and sleep disorders.

The NCS DR budget is a line item on the NHLBI administrative budget and includes the director, a public health analyst, an executive assistant, and an office assistant. From a separate NHLBI budget source, the NCS DR receives an allocation each year to support the activities of the Sleep Disorders Research Advisory Board and other programmatic activities, including workshops. Thus, the budget available to the director of the NCS DR is limited. The member institutes in the Trans-NIH Sleep Research Coordinating Committee provide support for their representative to the Committee, and NCS DR provides administrative support as needed for the Trans-NIH Sleep Research Coordinating Committee from its fiscal resources

already described. The Office of Prevention, Education, and Control support other NHLBI personnel who work on educational programs and two such individuals (personal communication, M. Twery, NIH, January 24, 2006).

The Advisory Board of the National Center on Sleep Disorders Research

The original NCSDR authorizing legislation established an advisory board to the NCSDR, composed of 12 members of the public—8 scientific members and 4 public members who either are advocates for or have a particular sleep disorder. Included in the advisory board are 10 ex officio members who represent relevant federal agencies (Table 8-2). The advisory board meets biannually. As directed in the authorizing congressional language “The advisory board shall advise, assist, consult with, and make recommendations to the Director of the National Institutes of Health and the Director of the Center concerning matters relating to the scientific activities carried out by and through the Center and the policies respecting such activities, including recommendations with respect to the [research] plan” (U.S. Congress, Senate, 1993). As will be discussed in further detail below, throughout the 12 years since its establishment the advisory board has had varying levels of activity in these responsibilities.

Since its inception, the advisory board has had 29 members. It is NIH policy that the appointed members of advisory councils or other mandated boards cannot serve for terms of more than 4 years and that reappointment is not permitted. This presents a strain on a small field such as somnology and sleep medicine, as those most knowledgeable about the field are frequently selected. It is important that the composition of the advisory board consists of members who are credible and who have the respect of the somnology and sleep medicine community, as well as an understanding of large research and educational enterprises, background as a practicing

TABLE 8-2 Ex Officio Members of the NCSDR Advisory Board

Director of the National Institutes of Health (NIH)
Director of the National Center on Sleep Disorders Research (NCSDR)
Director of the National Heart, Lung, and Blood Institute (NHLBI)
Director of the National Institute of Mental Health
Director of the National Institute on Aging
Director of the National Institute of Child Health and Human Development
Director of the National Institute of Neurological Disorders and Stroke
Assistant Secretary for Health
Assistant Secretary of Defense (Health Affairs)
Chief Medical Director of the Veterans Affairs (VA)

researcher, and awareness of a wide variety of public policy issues. Individuals who have been involved in the advisory board are provided in Appendix E, together with, where appropriate, their academic honors and area of expertise. As a result of the small numbers of senior members in the field, the tradition of academic leadership has been difficult to maintain on the advisory board. The board would benefit from advice made by senior investigators who have credibility and a sound understanding of both scientific and clinical advances, as well as an appreciation for policy issues. It is the opinion of this committee that after an appropriate interval senior members of the somnology and sleep medicine fields should be permitted to be reappointed to serve an additional term on the advisory board, along with the most promising juniors member of the field. This should be permitted until the field has a large enough cadre of experienced leaders.

NATIONAL SLEEP DISORDERS RESEARCH PLAN

One of the requirements of the advisory board is to periodically develop a comprehensive research plan. The first research plan was published in 1996. Its recommendations were based on analyses of the needs of the field and the investment in sleep-related programs by the federal government. The recommendations reflected the need to support three areas of research: (1) basic research using state-of-the-art approaches to elucidate the functions of sleep and the fundamental molecular and cellular processes underlying sleep; (2) patient-oriented research to understand the cause, evaluate the scope, and improve the prevention, diagnosis, and treatment of sleep disorders; and (3) applied research to evaluate the scope and consequences of sleepiness and to develop new approaches to prevent impaired performance during waking hours (NHLBI, 1996). Sixteen specific recommendations were crafted in such a way that the outcomes of the effort were easily measurable (see grant analysis below).

The second research plan, published in 2003, provided a brief overview of each topic area and an update of the research progress made since the 1996 report. The report contained over 191 individual recommendations. It has yet to be established, but the large number of recommendations may decrease the effectiveness of the document. The report did provide relative weight to some recommendations, but this may limit the implementation of the remaining recommendations. Based on the recommendations the advisory board identified a limited number of research priorities:

- Understand the neurobiology and function of sleep.
- Assess the impact of reduced sleep across age.
- Find the causes of various sleep disorders.
- Establish normative standards for sleep need and sleep variables.

- Discover/improve treatments for sleep disorders.
- Study if sleep disorders are associated with, and how they affect, the progression of other diseases.
 - Educate health care professionals and the public about healthy sleep habits and sleep disorders.
 - Apply novel technologies to the study of sleep.
 - Develop data and examine prevention, intervention, treatment, and other sleep-related programs specific to women and minorities.

In the research plan, training was considered the highest priority and a separate category was created to underline its importance.

Although the 2003 plan is more comprehensive than the 1996 plan, it lacks specificity in each recommendation, and no strategy was established to advance the research agenda. The large number of recommendations and the broad focus make it difficult to establish measures to evaluate the research plan's effectiveness. The 2003 research plan laid out an ambitious set of priorities but did not provide a strategy to implement the recommendations.

Scientific Advances Since the 2003 Sleep Disorders Research Plan

Below is a brief update of the state of science since 2003. However, as only 2 years have passed since the publication of the 2003 plan, this review is not meant to serve as an in-depth evaluation of the plan or an in-depth review of the current state of the field. Rather, its purpose is to demonstrate the potential the field has to continue to make great scientific strides. The outline for this update uses the organization originally used in the executive summary of the 2003 National Sleep Disorders Research Plan. As the following sections will demonstrate, although there has been scientific progress leading to an even greater number of unanswered questions, over the last few years the field has not grown but has reached a plateau.

Circadian Neurobiology

Research in this area is expanding because of advances in basic research. The major molecular and anatomical components associated with the generation of circadian rhythms have been known for about a decade. Genetic variants associated with delayed and advanced sleep phase are increasingly reported in a small minority of patients with familial occurrence (Xu et al., 2005). However, the clinical implications of altered circadian rhythms are yet to be explored. Some examples include the need to better define the causes and consequences of delayed phase in adolescence and to understand advanced phase in the elderly (Carskadon et al., 2004; Monk, 2005).

The importance of circadian rhythms extends beyond the brain. It is now recognized that the circadian clock does not solely operate within the suprachiasmatic nucleus but also at multiple levels in peripheral and central organs (Yamazaki et al., 2000; Yoo et al., 2004). Researchers have continued to elucidate with increasing detail the molecular mechanisms regulating these multiple molecular clocks. For example, peripheral clock markers can now be generated and studied in human fibroblasts (Brown et al., 2005). In addition, the genetic disruption of molecular mechanisms regulating circadian rhythms is recognized as deleterious at multiple levels within the organism. For example, the *Clock*-mutated mouse was found to suffer from metabolic abnormalities and to be prone to obesity (Turek et al., 2005). It is also increasingly likely that *Clock* genes have effects on the sleep process itself. This research may explain, for example, why shift workers are prone to certain diseases (Harrington, 1994; Boggild and Knutsson, 1999).

Sleep Neurobiology and Basic Sleep Research

The importance of the hypothalamus in sleep regulation, beyond the generation of circadian rhythms and their genesis within the suprachiasmatic nuclei, is increasingly clear (Saper et al., 2005). The recognition of the ventrolateral preoptic area as a sleep generator, together with the identification of the hypocretin (orexin) system as a wake promoting system, has fueled intense research in this area. How these two systems interact neuroanatomically, and how they affect other classical neurobiological systems, such as the monoamine and cholinergic systems, is being elucidated (Saper et al., 2005). Projection sites and novel sleep regulatory nuclei are being identified. The impact of this research is being felt beyond the field; for example, the role of the hypocretin system in regulating dopaminergic systems and addiction potential for drugs of abuse is the subject of intense investigation (Harris et al., 2005).

The function of sleep is also increasingly explored through phylogenetic approaches—the study of sleep in various animal species (Rattenborg et al., 2004; Lyamin et al., 2005). Sleep is a vital behavior conserved across evolution, suggesting it serves one or more critical functions. One important function may be the development of the neonatal brain, as many animals sleep a lot just after birth. The necessity of sleep may also be seen in animals that are in constant motion (e.g., swimming aquatic mammals or migrating birds) as they have developed unihemispheric sleep to allow for the generation of sleep under these difficult ecological circumstances. Interestingly, several reports are now suggesting that in specific instances, sleep can be suppressed completely for very long periods (up to months), such as during long-range migration in certain birds (Rattenborg et al., 2004) or even more surprisingly just after birth in some cetaceans (Lyamin et al.,

2005). These recent results suggest it may be possible to sustain life without sleep in special circumstances, which challenges existing dogma and suggests an area ripe for further advances.

This field of research is also benefiting from genetic studies in animal models. Knockout mice models (mice that are bred so that they lack certain genes) are now systematically being evaluated for sleep abnormalities. Gene variants, including a number of variants that affect sleep, have been isolated in various mouse strains that have specific electroencephalogram patterns (Tafti et al., 2003). These and other genetic mechanisms should be explored in future studies (Maret et al., 2005).

Sleep Disorders in Neurology

The discovery in 1999 and 2000 that hypocretin/orexin is involved in the pathophysiology of most narcolepsy-cataplexy cases is now being translated into clinical practice. Measuring cerebral spinal fluid (CSF) hypocretin-1 (orexin-A) is used in some cases to diagnose narcolepsy and is listed as a diagnostic tool in the revised *International Classification of Sleep Disorders* (AASM, 2005; Bader et al., 2003; Mignot et al., 2003). This diagnostic procedure may be especially important considering the recent report of high prevalence of sleep onset during rapid eye movement (REM) sleep instead of during nonrapid eye movement (NREM) sleep in the general population, a finding that may suggest a large number of false positives for this test and/or a high prevalence of narcolepsy without cataplexy (Singh et al., 2005).

Sleep disturbances are recognized as a major issue in Parkinson's and Lewy body disease (Rye, 2004), also suggesting a role for dopamine in sleep regulation. Not only can Parkinson's disease patients have a narcolepsy-like daytime sleepiness, but REM behavior disorder is now recognized as an important component of these disorders, often preceding Parkinson's disease by several decades. Investigators are also increasingly interested in other disorders where hypocretin abnormalities might explain sleep disturbances (Nishino and Kanbayashi, 2005), most notably Huntington's chorea, a disorder where mice models show a preferential hypocretin cell loss (Petersen et al., 2005). Similar sleep studies are also occurring with Alzheimer's dementia and stroke patients, where central and obstructive sleep apnea (OSA) may play an important role in both causing and exacerbating the condition.

Finally, rapid progress is occurring in our understanding of restless legs syndrome (Trenkwalder et al., 2005). Pathophysiology and treatment may be closely linked to the dopaminergic system and iron metabolism. Genetic studies suggest the existence of at least three potential loci, located on chromosomes 12, 14, and 9, and investigators are narrowing down on possible candidate genes. It is likely that those actually causing diseases will soon be identified (Manconi et al., 2004).

Sleep-Disordered Breathing

Genetic epidemiological studies conducted over the prior decade have clearly established that sleep-disordered breathing, although a complex trait, has a strong genetic basis with evidence of oligogenic inheritance (Buxbaum et al., 2002). Areas of linkage for the apnea-hypopnea index (AHI) appear to differ by ethnicity (Palmer et al., 2003, 2004). Association and fine mapping studies have quantified the potential role of several candidate genes in the pathogenesis of sleep apnea (Gottlieb et al., 2004b; Larkin et al., 2005a), with results implicating a gene near the *APOe4* locus (Larkin et al., 2005a). There is also evidence that sleep-disordered breathing and obesity, a major public health problem, are partly linked by pleiotropic genetic mechanisms (Palmer et al., 2003, 2004). Thus, future studies of the genetics of sleep-disordered breathing also likely will illuminate the genetic basis of obesity. Applying advances in genome association methods to population studies of sleep apnea will be important in discovering genes for this and related diseases.

Large scale epidemiological studies in the 1990s quantified the prevalence of OSA in middle aged and elderly populations (Ancoli-Israel et al., 1991, 1995; Young et al., 1993). More recently, population-based studies also identified sleep-disordered breathing to be common in American school-aged children, with an especially high prevalence in African American children (Rosen et al., 2003). Other studies have identified the predilection of other groups to sleep apnea. These include commercial drivers (Howard et al., 2004), whose occupations place them at particular risk for sleepiness-associated injuries (Gurubhagavatula et al., 2004). Further work is needed to develop and apply screening approaches for identifying individuals at high risk for sleep apnea (see technology section). However, in the case of commercial drivers, a two-stage screening strategy using questionnaires and simplified tests was shown to be effective (Gurubhagavatula et al., 2004). Given that commercial drivers with sleep apnea are likely to be at an increased risk for crashes, occupational screening of this group may provide an important opportunity to test the model for occupational screening for sleep disorders.

There is developing evidence that sleep apnea leads to oxidative stress (Lavie, 2003). This likely results from the cyclical doxygenation-reoxygenation, akin to ischemia reperfusion, that occurs with apneic events, causing free radical production and increased levels of inflammatory molecules. C-reactive protein, a biomarker for cardiovascular disease, may be elevated in OSA. C-reactive protein declines with treatment with continuous positive airway pressure (CPAP) (Yokoe et al., 2003). Increasing oxidative stress is not only relevant to the cardiovascular risk of sleep apnea but also to its effects on neurocognition. Cyclical intermittent hypoxia leads to oxidative damage of various groups of

neurons: hippocampal neurons with resulting learning deficits (Row et al., 2003); hypoglossal motoneurons, a mechanism that may accelerate disease progression (Veasey et al., 2004b), as well as wake active neurons (Veasey et al., 2004a). The latter may be the mechanism by which residual sleepiness occurs in patients with OSA even when they are well treated with nasal CPAP.

There is ongoing evidence from prospective studies that OSA is a risk factor for cardiovascular events and mortality, and this evidence is becoming more compelling based on large prospective cohort studies. Such studies show that patients with sleep apnea, in particular severe sleep apnea (i.e., AHI greater than 30 episodes per hour), have increased rates of cardiovascular events, strokes, mortality independent of other risk factors, and hypertension (Yaggi et al., 2005; Marin et al., 2005). Patients with severe sleep apnea who were not treated have an increased rate of cardiovascular events and deaths compared to controls with similar degrees of obesity who do not have sleep apnea (Marin et al., 2005). When patients with severe sleep apnea are treated with CPAP, both the rate of cardiovascular events and cardiac deaths drop to control rates (Marin et al., 2005). Although this provides strong support for a role of OSA in atherogenesis, the critical proof for a causal association, and further defining a need for early treatment, requires randomized trials designed to assess the impact of OSA on cardiovascular events.

The Sleep Heart Health Study has added further support for sleep apnea being a risk factor for insulin resistance independent of the effects of obesity (Punjabi et al., 2004). In this large study the presence of sleep apnea (i.e., AHI greater than 15 events per hour) was independently associated with insulin resistance even after controlling for body mass index and waist-to-hip ratio, a measure of visceral obesity (Punjabi et al., 2004). Moreover, data suggest that treating patients with OSA by nasal CPAP significantly increases insulin sensitivity as measured by the euglycemic clamp method (Harsch et al., 2004). This effect was, however, most evident in relatively nonobese subjects, with questions regarding the extent to which sleep apnea treatment improves glucose tolerance in obese individuals with sleep apnea and may help prevent diabetes. A small study suggests that this is so; improvement is particularly found in those with high levels of a specific type of hemoglobin that is a marker for poor glucose control (Babu et al., 2005).

Although much of the focus of research continues to be on OSA, progress is also being made in other aspects of sleep-disordered breathing. Obesity-hypoventilation syndrome, a condition in which individuals hypoventilate during sleep (due to an increased respiratory load from the increased weight) and have elevated daytime arterial PCO_2 levels, has been shown to be common yet frequently unrecognized in obese hospitalized

patients. Obese patients with this problem have poorer medical outcomes (Nowbar et al., 2004).

Thus, this research in sleep and sleep disorders is vibrant and has great potential to improve public health problems related to sleep-disordered breathing.

Insomnia

A turning point in this area may have been the recent NIH-sponsored State-of-the Science Conference on chronic insomnia (Dolan-Sewell et al., 2005). In this conference, a decision was made to abandon the concept of secondary insomnia. The rationale for this change was that it is difficult in most cases to distinguish causes and consequences for insomnia. The possibility that insomnia is associated with abnormalities of sleep microarchitecture and brain metabolism, as measured by imaging studies, is also increasingly recognized. This, together with the concept of hyperarousal in patients with insomnia (Nofzinger et al., 2004), is leading to the discovery of objective markers and a pathophysiological model for insomnia. It was also recognized that insomnia is not only frequently associated with depression but may be an independent predictor of it (Roth and Roehrs, 2003).

Treatment modalities for insomnia are changing. Prescribed hypnotic use is reported in children and adolescents, a pattern that raises concern as there are limited data in this area (Owens et al., 2003). An increasing number of well-designed studies are showing efficacy and safety for cognitive-behavioral therapies (Morin, 2004). This, together with the introduction and development of a large number of new hypnotics of various modes of action, is changing clinical practice in insomnia.

Pediatric Sleep Sciences

There have been several advances in the field of pediatric sleep medicine in the last two years: the discovery of the gene for congenital central hypoventilation syndrome, improved understanding of the pathogenesis and epidemiology of sleep apnea, and better understanding of the complications associating OSA in children. However, pediatric sleep remains relatively understudied, and there are still many gaps in the knowledge base. For example, although the Back to Sleep Campaign has been very successful there is still very little information concerning the etiology of sudden infant death syndrome (SIDS).

In 2003, Amiel and colleagues described a mutation of the *PHOX2B* gene in 62 percent of their patients with congenital central hypoventilation syndrome (Amiel et al., 2003). Following refinement of the technique, 97

percent of patients have been shown to have a mutation of the gene (Weese-Mayer et al., 2003), which is dominant and usually a *de novo* mutation. This finding has already become useful in clinical practice, with clinical testing and amniocentesis now available.

There has been increasing research in the area of pediatric sleep-disordered breathing. Several studies have provided a better understanding of the pathophysiology of OSA in children, including the role of upper airway reflexes in this disease (Gozal and Burnside, 2004; Marcus et al., 2005). Major advances have been made in understanding the complications of childhood OSA. In particular, work from a number of different labs has shown that very mild obstructive apnea, and perhaps even primary snoring, is associated with changes in neurocognitive and behavioral function in children (Fregosi et al., 2003; Rosen et al., 2004; Gottlieb et al., 2004a). Other studies have shown that childhood OSA is associated with cardiac hypertrophy (Amin et al., 2005), inflammation (Tauman et al., 2004; Larkin et al., 2005b), and the metabolic syndrome (de la Eva et al., 2002), potentially putting children at risk for cardiovascular complications later in life. Of great interest is the observation of adverse outcomes in individuals with a very mild sleep apnea (including habitual snoring without appreciable levels of overnight hypoxemia). Given that almost all of the work to date has been descriptive, it is imperative that interventional studies assess whether early diagnosis and treatment would modify short- or long-term health outcomes. In this regard, there is also a need to identify the efficacy of sleep apnea treatment in children, including tonsillectomy and adenoidectomy, for which there has not yet been a single randomized controlled study of treatment for sleep apnea.

Sleep Deprivation

The impact of sleep deprivation and shift work on driving and industrial accidents has been known for more than a decade. Unfortunately, change, especially in the area of commercial driving, has been difficult to implement. Modafinil, a wake-promoting agent, may be effective for the treatment of shift work disorder and prove to be useful in this setting (Czeisler et al., 2005). Sleep deprivation is also increasingly recognized as being associated with poor school performance, especially when school re-starts after an extended number of days off. This may be mediated by delayed sleep phase, early school start time, and increased sleep need during adolescence (Carskadon et al., 2004).

Recent studies have shown that sleep deprivation causes medical errors among physicians (Lockley et al., 2004; Landrigan et al., 2004; Barger et al., 2005). Attentional lapses and errors can be improved by reducing work hours and increasing sleep (Lockley et al., 2004; Landrigan et al., 2004).

These findings are leading to rapid changes in the on-call requirements for physicians in training (Cavallo et al., 2004).

The impact of chronic sleep restriction on human health and endocrinological status is also increasingly recognized. Associations among short sleep, obesity, diabetes, and mortality have been reported (Alvarez and Ayas, 2004; Gottlieb et al., 2005). A large number of studies have shown cross-sectional association between short sleep and obesity (Cizza et al., 2005). A trend for a longitudinal association between shortening sleep and gaining weight is also typically found. The biological mediation of these changes may be through alterations in leptin and ghrelin, two major appetite regulatory hormones (Taheri et al., 2004; Spiegel et al., 2004). The levels of these hormones are altered in health subjects if sleep is restricted for a few nights.

Sleep Education and Training

Although a top priority of the 2003 research plan, the NIH has not established any new large-scale programs in training or career development. In fact, as has been described in Chapter 7, there has been a decrease in the number of career development grants pertaining to sleep. Further, although a few private foundations and professional societies have invested some in professional development, as discussed in Chapter 5, increased efforts are required to fully embrace the need to increase education and training programs. Thus, progress in this critical area has been quite limited.

ANALYSIS OF NIH-SPONSORED RESEARCH PROJECT GRANTS

Currently, assessment of the success of the sleep research effort at NIH seems to be based largely on the total dollars being committed by various institutes to the field (for more information see the 2001 to 2004 annual reports of the Trans-NIH Sleep Research Coordinating Committee). NIH funding for somnology research has increased by more than 150 percent since the NCSDR became fully operational in 1996, reaching a total of \$196.2 million (0.07 percent of the NIH budget) in fiscal year 2004 (NHLBI, 2003). However, this growth occurred during the same period that the overall budget to the NIH doubled.

At the same time that the science and magnitude of the problem requires greater investment, over the last few years NIH funding to sleep-related activities has plateaued. This has partially overlapped the period when the overall NIH budget has plateaued. Consequently, the future outlook for somnology and sleep medicine is unclear. In 2004, for the first time since the NCSDR was established, there was a decrease of \$846,000 in annual expenditures for sleep-related projects. This decrease raises even greater concern because it occurred in the same year that the NCSDR in-

cluded the expenditures of three additional institutes not included in previous fiscal reports. A comparison of research funding for the institutes in 2003 fiscal year analysis reveals a decrease of \$1.142 million. Further, between 2003 and 2004 there were fewer research project grants funded, and this trend may continue as the number of new research project grants funded in 2004 also decreased (Appendix G). There must be incremental growth in this field to meet the public health and economic burden caused by sleep loss and sleep disorders.

It is difficult to accurately track the commitment of different NIH institutes to somnology and sleep disorders, in part because there is no uniform accounting system. Some NIH institutes count only a proportion of a grant when only a component of the grant is related to sleep research, but others count the entire grant, even though sleep-related research is only a minor part of the grant. This is particularly problematic for large program project or center grants. More important, however, these financial data do not allow the advisory board or leadership of the NCS DR to track the type of research being conducted and hence help identify areas of need. Originally the NCS DR Advisory Board took an active role in assessing the then current portfolio of sleep research grants, such as the analysis that was published in the journal *Sleep* in 1999 (Gillette et al., 1999). The committee presents its analysis below and urges the advisory board to continue to take an active role in this and perform a similar analysis on an annual basis.

Somnology and Sleep Disorders RFAs and PAs

The 1996 research plan was based on analyses of currently funded grants and led to a number of specific RFAs and PAs. Recently, there has been a marked reduction in the number of sleep-related RFAs that provide an important mechanism to develop research programs in specific areas of need. They identify a narrowly defined area for which one or more NIH institutes have set aside funds for awarding grants. This is different from PAs, which identify areas of increased priority or emphasis but typically do not have specific funds set aside (except for PAS announcements).

Over the last 3 years, the NCS DR has only sponsored two programs, one PA and one RFA—Research on Sleep and Sleep Disorders: PA-05-046 (in 2004) (NIH, 2004) and Mechanisms Linking Short Sleep Duration and Risk of Obesity or Overweight: RFA-HL-06-003 (in 2005) (NIH, 2005). The marked reduction over recent years in efforts identifying and developing RFAs and PAs is seen by examining the list of RFAs and PAs in sleep disorders research since the inception of the NCS DR (Appendix F).

The recent efforts of the NCS DR can be compared to those of the National Center for Medical Rehabilitation Research (NCMRR), which is a similarly structured center in the National Institute of Child Health and

Human Development. The NCMRR supports research on enhancing the functioning of people with disabilities in daily life. Compared to the 1 RFA established by the NCSDR in fiscal year 2004, the NCMRR established 6 RFAs and 4 PAs. Further, between 2001 and 2004 the NCMRR established 20 RFAs, while the NCSDR established only 4 RFAs. It is unclear why there is such a dramatic difference in the activity of these two centers.

Protocol for Research Project Grant Analysis

This committee performed a detailed analysis of the 1995 and 2004 portfolios of NIH somnology and sleep disorders research project grants (R01) to determine the current investment in the field and to examine how the grant portfolio has changed over the last 10 years. To do so, abstracts of all sleep-related R01s in the Computer Retrieval of Information on Scientific Projects (CRISP) database were analyzed. This database collects information on the number of federally funded biomedical research projects. Sleep-related R01s were collected by searching the CRISP database for all abstracts that were classified under the following thesaurus terms: *insomnia*, *periodic limb movement disorder*, *restless legs syndrome*, *circadian rhythm*, *SIDS*, *sleep disorder*, *narcolepsy*, *sleep apnea*, *sleep*, *hibernation*, and *dream*. To limit the number of grants that were not relevant to somnology or sleep disorders, the committee only included grants in which the key words appeared in both the thesaurus terms and abstract and not the abstract alone. It should be noted that the following conclusions are based on the number of grants awarded in each area. The committee did not have access to the applications that were submitted and not funded; therefore, it is not possible to conclusively determine if changes in investment are the result of NIH policy, the number and/or quality of submissions in each area, composition of grant review committees, or a combination of these factors.

General Findings

The CRISP search identified 156 sleep-related grants for 1995 and 397 for 2004. Upon review of their abstracts a number of these were determined to be unrelated to sleep. This resulted in 116 total sleep-related grants in 1995 and 331 sleep-related grants in 2004, a 2.85 fold increase (Table 8-3). The number of the grants deemed not relevant to sleep-related research—34 out of 156 in 1995, and 59 out of 397 in 2004—represents a relatively constant percentage (i.e., 21 percent and 15 percent, respectively; supplemental grants and grants with no abstract were also not classified). Thus, use of this methodology to track temporal trends in number of grants seems appropriate. Of the relevant sleep R01 grants there were 253 principal

TABLE 8-3 Analysis of Somnology and Sleep Disorders Research Project Grants (R01): 1995 and 2004

	1995		2004		Number in 2004 / Number in 1995
	Number of Sleep Grants	Percentage of Sleep Grants	Number of Sleep Grants	Percentage of Sleep Grants	
Grants Analyzed					
Number of grants analyzed	156		397		2.54
Number of grants relevant to sleep	116		331		2.85
Number of principal investigators	100		253		2.53
Clinical or Basic Research					
Clinical research projects	71	61	179	54	2.52
Basic research projects (not circadian rhythm)	28	24	61	18	2.18
Circadian rhythm projects	19	16	97	29	5.11
Type of Sleep Disorder					
Restless legs syndrome and periodic limb movements	0	0	5	2	N/A
Insomnia	10	9	22	7	2.20
Narcolepsy/hypersomnia	5	4	6	2	1.20
Circadian rhythm	7	6	22	7	3.14
Parasomnia	1	1	0	0	N/A
Sleep deprivation	3	3	18	5	6.00
Sleep apnea	19	16	65	20	3.42
Sleep neurological, other	3	3	6	2	2.00
Drug abuse	2	2	11	3	5.50
Sleep medical, other	15	13	23	7	1.53
Sleep psychiatric disorder	13	11	10	3	-0.23

Research Strategy								
Systems neuroscience	32	28	62	19	1.94			
Electrophysiology	26	22	70	21	2.69			
Pharmacology	13	11	36	11	2.77			
Cell biology	27	23	57	17	2.11			
Molecular	10	9	70	21	7.00			
Genetic	5	4	53	16	10.60			
Observational study	36	31	84	25	2.33			
Intervention study	22	19	54	16	2.45			
Epidemiology	10	9	24	7	2.40			
Hormone/biomarker	13	11	71	22	5.46			
Clinical trial	12	10	27	8	2.25			
Assessment of devices	4	3	5	2	1.25			
Species								
Human, no age specified	26	22	68	21	2.62			
Human, child and adolescent	12	10	23	7	1.92			
Human, adult	18	16	51	15	2.83			
Human, elderly	17	15	30	9	1.76			
Rat	21	18	77	23	3.67			
Mouse	2	2	32	10	16.00			
<i>Drosophila</i>	2	2	15	5	7.50			
Other or not specified	32	28	60	18	1.88			

NOTE: Percentages were rounded. N/A = Not applicable.

investigators in 2004, a 2.53 fold increase from 1995 (100 principal investigators). Given that an estimated 50 to 70 million Americans have sleep-related health challenges, the current investment of 0.07 percent of the NIH budget and presumably a lesser proportion across other agencies, we believe, is not sufficient.

Clinical, Basic, and Circadian Rhythm Research Projects

Each grant was categorized to determine if the research was primarily basic or clinical in nature. Fifty-four percent of the grants in 2004 focused on clinical sleep disorders. Seventeen percent of 2004 grants were focused on basic sleep research projects, and 29 percent were devoted to the study of circadian rhythms. The total percentage of nonclinical research projects devoted to circadian rhythms rose from 40 percent of nonclinical research projects in 1995 to 61 percent in 2004. There has been over the last 10 years a disparate growth in these areas. Investment in circadian rhythms research projects increased by 5.11-fold; however, basic research unrelated to circadian rhythms only increased by 2.53-fold, well below the need. Not surprisingly, this largely reflects where much scientific advance has occurred.

Sleep Disorders

Since 1995, there has also been growth in the number of grants focused on sleep disorders. The current analysis suggests that research funding is disproportional to the public health burden and the known prevalence and consequences of the disorders. In a few cases, research has actually decreased or barely grown. These areas include parasomnia research (from one grant in 1995 to none in 2004), sleep in psychiatric disorders (0.23-fold decrease), and narcolepsy (1.20-fold increase). The lack of research regarding parasomnias is troublesome, considering the prevalence of these conditions. Similarly, the decrease in research grants in the area of sleep disturbances in psychiatric diseases is disturbing, considering the growing recognition that insomnia is a major risk factor for depression (see the Scientific Advances Since the 2003 Sleep Disorders Research Plan). This last observation should be mitigated by the relatively hefty increase in insomnia research.

Research in the area of narcolepsy and hypersomnia sleep disorder research also stayed flat. This last finding was disappointing, considering the recent discovery of hypocretin deficiency as the main cause of narcolepsy with cataplexy and the growing recognition that a large number of patients have milder forms of centrally mediated hypersomnolence, narcolepsy without cataplexy, and idiopathic hypersomnia. Research in this area may be uniquely poised to make progress, but funding has not increased. Not a

single grant was identified on the study of idiopathic hypersomnia or Kleine-Levin syndrome. The latter is admittedly a rare condition.

Over the 10-year span between 1995 and 2004 there has been no growth in research examining the etiology and pathophysiology of SIDS. In 1995 seven R01s were identified as focusing, at least partially, on SIDS, but in 2004 there were only six grants. Although the prevalence of SIDS has decreased since the Back to Sleep public education campaign began, this is still an area of research that warrants attention.

Selected areas grew more rapidly. There has been increasing interest in restless legs syndrome/periodic leg movements research; but the current investment is still low. There were no grants with a primary focus in these areas in 1995 and six in 2004. Given the high prevalence of restless legs syndrome and its negative impact (Chapter 3), the small number of grants is, however, still surprising. Further, although the number of insomnia research project grants has also grown from 10 grants in 1995 to 22 grants in 2004 (2.20-fold growth), this growth is modest given the high prevalence of insomnia. Clinical research project grants focused on the elucidation of sleep apnea demonstrated an increase in support that is reflected in the increased appreciation of its public health burden that occurred over the same period—19 grants in 1995 (15 percent of total grants) and 65 in 2004 (22 percent of total grants), a growth of 3.42-fold.

Assessment of Devices

The committee also noted that research assessing new devices barely grew from 1995 to 2004 (1.25-fold increase). This was also a troubling trend, as the study group identified the need to validate and increase the use of ambulatory monitoring devices in the diagnosis and assessment of sleep disorders, most notably sleep-disordered breathing (see Chapter 6).

Research Strategy

The committee also examined the primary research strategy proposed in each project. The striking trends in this area have been the dramatic growth in studies employing molecular (7.00-fold growth) and genetic (10.60-fold growth) strategies. Although this partially reflects the trends in modern biomedical research, the NHLBI, the National Institute of Mental Health, and the National Institute of Child Health and Human Development sponsored an RFA in 1996 to advance the understanding of the molecular and genetic basis of sleep and sleep disorders (RFA-HL-96-015). This RFA provided researchers funding for research projects that had molecular and genetic strategies.

Species

In this area there are also key trends. The growth in studies using mice is staggering, 16-fold from 1995 to 2004. There were only two grants using mice in 1995 and 32 in 2004. This is likely to be in direct response to the NHLBI, the National Institute of Mental Health, the National Institute on Aging, and the National Institute of Neurological Disorders and Stroke sponsoring an RFA in 1998 to develop improved molecular, cellular, and systems approaches to investigate sleep and circadian phenotypes in mice (RFA-HL-99-001).

There has also been a major increase in studies utilizing *Drosophila* as a model organism (7.50 fold increase). The use of *Drosophila* to study sleep was originally recommended at a workshop held by the NCSDR in 1995 and was included in the previously mentioned 1996 RFA to advance the understanding of the molecular and genetic basis of sleep and sleep disorders (RFA-HL-96-015). There are also a large number of grants that are in the "Other" category for species.

There are, as expected, a large number of studies on humans. The total number of grants in humans in 1995 was 73, but in 2004 it was 172, a 3.35-fold increase. It is concerning, however, that there are still only 23 grants studying sleep and its disorders in children and adolescents. This represents only 13 percent of total grants in humans, and the increase in pediatric sleep grants (1.92-fold) is lower than that for all grants (2.35-fold) and for all grants in humans (3.35-fold increase). The number of grants studying sleep and its disorders in the elderly, a population with a particularly high prevalence of sleep disorders, is also only 30. The growth in this area (1.77-fold) is also less than in other categories. Finally, although there has been growth in human subjects research, there has been a limited number of long-term clinical outcomes intervention studies that have examined strategies to improve the scientific base and treatments.

Composition of Grant Review Panels

An analysis of relevant NIH review panel expertise was also performed. To do so, the composition of review panels that received applications with sleep was analyzed. A total of 24 review panels, including special emphasis panels and standing integrated review groups (IRG), were included. Reviewers were subjected to Medline searches with the keywords *sleep* and *circadian*. Names were also visually inspected by multiple members of the committee who had expertise in various aspects of somnology and sleep medicine. Membership to sleep or circadian rhythms societies was noted, together with area of expertise. Only reviewers with a major sleep or circa-

dian research focus, as judged by their publication record or professional society, were considered.

Twenty-eight reviewers with knowledge in sleep or circadian biology were identified in the 24 review panels. It is important to note that although some review panels may not have experts in the field, often the Center of Scientific Review will appoint ad hoc reviewers when specific expertise is absent on the review panel. One third of the reviewers (12 out of 36 reviewers) were concentrated in a single study section, the Biological Rhythms and Sleep Study Section. Another third (9 reviewers) were in NHLBI special emphasis panels. Eleven of the total 28 (39 percent) reviewers were primarily interested in circadian rhythm research, rather than basic sleep research or clinical sleep disorders. Four other NHLBI review panels had more than 2 reviewers with sleep and circadian expertise; these included the mentored patient-oriented carrier development (K23) grant review panel (2 reviewers); a NHLBI special emphasis panel on T32 grants (2 reviewers); a small business activities special emphasis panel (4 reviewers) and the Respiratory Integrative Biology and Translational Research panel (2 reviewers). It was notable that two study sections with *sleep* in their title (and mandate) had one or no reviewers with a sleep expertise: the Neural Basis of Psychopathology panel, addictions and sleep disorders (1 reviewer); and the cardiovascular and sleep epidemiology study section (no reviewers with sleep expertise).

As expected, there was an association between reviewer expertise and types of grants funded. A notable finding was the low percentage of reviewers with clinical research expertise (36 percent) covering all of the different sleep disorders outlined in earlier chapters. This finding may be one potential reason why clinical research was the area with the least growth. However, because the committee was unable to examine and categorize all the grants that were submitted and not funded, it is difficult to interpret this finding. Further, the limited number of sleep reviewers, as well as the small number of funded grants, may also be a direct reflection of the limited number of scientists (especially senior investigators) in specific areas of this field.

Value of Grant Analysis Protocol

Categorizing each research project grant offers researchers and policy makers the opportunity to examine the current investment in particular areas, identify areas in need of greater investment, and provide a quantifiable metric to examine the success of specific RFA and PA programs. This committee strongly encourages the NCS DR Advisory Board to perform a similar annual analysis of all somnology and sleep disorders grants, including research (R), training (T), fellowship (F), career development (K), pro-

gram (P), and cooperative (U) activities sponsored by the NIH, the CDC, and Department of Defense, Department of Transportation, Department of Labor, and other relevant federal agencies. This committee also believes that the Center for Scientific Review should gather basic keyword information on submitted grants and reviewers to address adequacy of review expertise on review panels. This information would be helpful to the NIH at large and to the NCS DR as it develops a more proactive research plan.

Although the success of an RFA is dependent on the number and quality of grant applications, this analysis demonstrates the value an RFA may have in expanding interest and awareness in specific areas of a field. Therefore, this committee recommends that the NCS DR Advisory Board use their annual analysis to identify priority research and training areas and annually recommend an RFA to appropriate advisory councils of the Trans-NIH Sleep Coordinating Committee and other federal agencies including the CDC.

NEXT STEPS IN ACCELERATING PROGRESS

Given the multiple and varied sources of federal and private funding and support for the field and the numerous disciplines involved in research and clinical care, the challenge for the field of sleep medicine is to develop a collaborative and focused approach with a strong research infrastructure. To bolster clinical and basic research efforts, catalyze collaborative research efforts, and attract the breadth of talented researchers who will be able to move somnology and sleep disorders research and clinical care forward to achieve the therapeutic solutions requires a coordinated and integrated strategy.

Strengthen the NCS DR and Its Advisory Board

It is an opportune time for coordination of sleep-related activities throughout the federal government. The NCS DR and its advisory board should take the lead in reinvigorating a coordinated strategy. To assist in this coordination, annually the directors of the NCS DR and the NCS DR Advisory Board should meet with all institute directors who are members of the Trans-NIH Sleep Coordinating Committee and directors of other relevant federal agencies. Further, institutes at the NIH that manage a large sleep-related portfolio should be encouraged to appoint appropriate representatives of the field of Somnology and Sleep Medicine to their advisory councils and program project review committees.

Recommendation 8.1: The National Center on Sleep Disorders Research and its advisory board should play a more proactive role in stimulating and coordinating the field.

The National Center on Sleep Disorders and Research (NCSDR) should have adequate staff and resources to ensure its ability to fulfill its mission of coordinating and stimulating training, research, and health information dissemination relevant to somnology and sleep disorders. All relevant institutes with significant sleep portfolios should become members of the Trans-NIH Sleep Research Coordinating Committee. Further, the NCSDR Advisory Board should take a more proactive role in advising the director of the NCSDR. On an annual basis, the NCSDR and its advisory board should:

- Identify specific objectives that address each of the three NCSDR missions and evaluate specific actions taken to accomplish each objective. This assessment should be reported in an annual meeting to the Trans-NIH Sleep Coordinating Committee, the institute directors of its members, and to the director of the NIH.
- Directors of the other federal agencies that fund significant sleep-related activities, such as Department of Defense, Department of Commerce, Department of Education, Department of Labor, and Department of Transportation should report annually on their activities to the NCSDR Advisory Board.
- The NCSDR Advisory Board should annually review the current NIH portfolio of sleep-related grants, as well as requests for applications, and program announcements, assess them for responsiveness to the program plan and identify gaps in research and training.
- The NCSDR Advisory Board should annually recommend new, or modify existing, requests for applications that can be presented to appropriate NIH institutes and other federal agencies including the Centers for Disease Control and Prevention and Department of Defense. Multiple members of the Trans-NIH Sleep Coordinating Committee are encouraged to continue to cosponsor sleep-related grants.

Enhance Research Collaborations

Clinical advances in treatments for chronic sleep loss and sleep disorders depends on the quality and integration of fundamental knowledge from multiple laboratory and clinical disciplines; including but not limited to: cardiology, dentistry, endocrinology, epidemiology, molecular biology,

neurology, neurosciences, nursing, nutrition, otolaryngology, pediatrics, pharmacology, psychiatry, and pulmonology. Historically the field has been clinically focused and has not integrated the efforts of its clinical and basic research scientists. For the field to make its next set of advances it will require a strengthened research infrastructure that will feature the development of combined clinical and research centers of excellence focused on somnology and sleep medicine and a structured network to facilitate and ensure collaborative interdisciplinary approaches.

Centers of excellence are required to establish and enhance somnology and sleep disorders research. A critical feature of these centers will be their ability to foster collaborations among the many research and clinical disciplines through a coordinated and integrated effort. They should promote interdisciplinary research, which is needed to explore the interrelationship between sleep and an individual's health (e.g., common medical illnesses). The proposed research network described below will integrate the efforts of the broad array of researchers (both investigators at centers of excellence and from other institutions) who study or are involved in somnology and sleep medicine and other relevant avenues of therapeutic intervention for chronic sleep loss and sleep disorders.

Establish Centers of Excellence

The committee urges a strong continued commitment by the NIH to designate and support Somnology and Sleep Medicine Centers of Excellence. These centers would provide the interdisciplinary environment that is essential to accelerate the development of future advances in treating chronic sleep loss and sleep disorders. They would facilitate interactions between laboratory, clinical, and population scientists. Further, the centers would create an environment to support cross-cutting research that requires collaboration among scientists who work in different intellectual contexts. These would not only be "research centers," but they would be sites for collaborations focused on the close association between research, clinical care, education, and dissemination of information.

Modeled after the National Cancer Institute's Cancer Center Program (NCI, 2004), these comprehensive centers of excellence would offer expanded laboratory facilities; focused interactions among preclinical researchers, clinical researchers, and patients; and central sites for clinical trial design. They would serve as the centerpiece of the nation's effort to reduce morbidity and mortality from chronic sleep loss and sleep disorders. This investment would likely draw new senior-level researchers into the somnology and sleep medicine field and would heighten the interest of young investigators in devoting their research interests to chronic sleep loss

and sleep disorders treatment. Further, structuring these centers to include strong integrated and coordinated clinical and basic research programs will help facilitate translational research. The centers would deliver medical advances to patients, educate health care professionals and the public, and reach out to underserved populations.

As described in detail in Chapters 5 and 7, enhancing career opportunities for researchers at all points in their careers is vital to accelerating progress in somnology and sleep medicine research. The committee believes that strengthening the research infrastructure through the development of new comprehensive centers will be the impetus needed to attract and retain early career, mid-career, and senior researchers. At these centers they will have the opportunity to fully engage in their own research initiatives, in addition to having the resources to develop and nurture trainees and sustain a full research effort.

These centers should be supported with the infrastructure needed to promote and enhance the institutional development of somnology and sleep medicine and treatment capabilities. This includes core research laboratory equipment, tools, and facilities; an emphasis on training programs; strong basic and clinical research components; and a structured plan for research priorities. However, the committee does not call on any specific organizational model, recognizing the diversity of academic settings that include well organized, freestanding centers; a center matrix within an academic institution; or a formal consortium under centralized leadership. The centers should also have the capacity to facilitate clinical trials; develop best practices and clinical guidelines; educate the community; screen and counsel individuals with chronic sleep loss and sleep disorders; and educate health professionals about state-of-the-art diagnostic, preventive, and treatment techniques. These centers of excellence should serve as the cornerstone of a National Somnology and Sleep Medicine Research and Clinical Network designed to coordinate and support somnology and sleep medicine research efforts.

Similar to the organization of the cancer centers, this committee envisions both Somnology and Sleep Medicine Centers and Comprehensive Somnology and Sleep Medicine Centers (NCI, 2004). Somnology and Sleep Medicine Centers should have a scientific agenda primarily focused on basic, population science, or clinical research, or any two of these three components. Similar to comprehensive cancer centers with a clinical component, the centers with clinical components are expected to conduct early phase clinical trials (NCI, 2004). A comprehensive somnology and sleep medicine center is expected to have reasonable depths and breadths of research in each of these areas. As with the National Cancer Institute designated comprehensive centers, Comprehensive Somnology and Sleep Medicine Centers are expected to disseminate information to the public and

health care professionals about medical advances developed within the center. They should also establish formal programs for teaching, screening, therapy, and/or preventative interventions.

As identified by the National Cancer Institute, there are six essential characteristics of a designated cancer center: facilities, organizational capabilities, interdisciplinary and transdisciplinary collaboration and coordination, cancer focus, institutional commitment, and center director (Box 8-1). Each of these attributes—substituting somnology and sleep medicine focus for cancer—is also likely to be critical for establishing and sustaining efficient and productive somnology and sleep medicine centers of excellence.

BOX 8-1

The Six Essential Characteristics of a National Cancer Institute-Designated Cancer Center

Facilities: Dedicated resources to the conduct of cancer-focused research and to the center's shared resources, administration, and research dissemination should be appropriate and adequate to the task.

Organizational capabilities: Adequate capacity for the conduct of research and the evaluation and planning of center activities should take maximum advantage of the parent institution's capabilities in cancer research.

Interdisciplinary and transdisciplinary collaboration and coordination: Substantial coordination, interaction, and collaboration among center members from a variety of disciplines should enhance and add value to the productivity and quality of research in the center.

Cancer focus: A defined scientific focus on cancer research should be clear from the center members' grants and contracts, and from the structure and objectives of its programs.

Institutional commitment: The center should be recognized as a formal organizational component with sufficient space, positions, and resources to ensure organizational stability and fulfill the center's objectives.

Center director: The director should be a highly qualified scientist and administrator with the leadership experience and institutional authority appropriate to manage the center.

SOURCE: National Cancer Institute (2004).

Develop Comprehensive Somnology and Sleep Medicine Centers of Excellence

The establishment of Somnology and Sleep Medicine Centers of Excellence requires large programs that can support and foster excellence in research, clinical care, and population science. This committee recognizes that there are few academic programs that currently have this capacity. However, to facilitate other academic centers achieving this goal, the NIH Exploratory Center award (P20) may be used for this endeavor. These awards are intended to facilitate the development of collaborative research teams of established investigators by providing support for collaborative research projects and core services for investigating leading-edge research questions not currently being addressed in optimal ways (NIMH, 2006). Further, the mechanism supports planning for new programs, expansion or modification of existing resources, and feasibility studies to explore various approaches to the development of interdisciplinary programs that offer potential solutions to problems of special significance (NIH, 2006a). Support is typically limited to 5 years and is not renewable.

The Silvio O. Conte Centers to Develop Collaborative Neuroscience Research provide a good example. These centers, supported through a P20 mechanism, support early-stage development of collaborative teams of high-caliber investigators from diverse disciplines to study basic and/or clinical neuroscience issues. They are characterized by the following:

- the capacity to bring together a team of collaborative investigators with different scientific perspectives.
- an organization that supports innovative creativity, and potentially high-risk/high-import research questions that require collaborative research.
- interactive research projects and core facilities to support projects.
- a program director with a demonstrated ability to organize, administer, and direct the center.
- opportunities for young investigators and close coordination between the center and relevant predoctoral and/or postdoctoral research training programs.
- outreach that makes the public aware of the importance and implications of the center's research.

A developing center must have a clearly articulated plan to develop a set of scientific core functions that will enhance and expand the capacity to move somnology and/or sleep disorders research and treatment into community settings.

NIH Institutional Clinical and Translational Science Award

The NIH has established the Institutional Clinical and Translational Science Award, which has the purpose of developing programs to overcome the growing barriers between clinical and basic research, facilitate the sharing of knowledge to the clinic and back again to the basic research laboratory, and aid academic institutes in developing efficient capabilities to perform clinical and translational science. Through these programs, the NIH aims to: (1) attract and develop a cadre of well-trained multi- and interdisciplinary investigators and research teams; (2) develop programs that spawn innovative research tools and information technologies; and (3) synergize multi- and interdisciplinary clinical and translational research and researchers to catalyze the application of new knowledge and techniques to clinical practice at the front lines of patient care (NIH, 2006b). As supported by all the same arguments already presented throughout this report, somnology and sleep medicine programs are ideal recipients.

As the NIH highlights, to ensure the successful establishment and long-term sustenance of these groundbreaking programs, it is important that the developed program accrue significant institutional support, be granted status as a major administrative entity within the applicant institution, and that the program director have authority, perhaps shared with other high-level institutional officials, over requisite space, resources, faculty appointments, protected time, and promotion (NIH, 2006b).

National Somnology and Sleep Medicine Research Network

A research network is of particular importance in the field because of the need for a coordinated interdisciplinary research approach to basic and clinical research, clinical care, public education, and training. The proposed National Somnology and Sleep Medicine Research Network would improve the efficiency and capacity to research on rare sleep disorders. The Somnology and Sleep Medicine Centers of Excellence discussed above would spearhead this dedicated focus on basic, clinical, and translational research and would promote collaborations among all sites conducting research relevant to somnology and sleep medicine. Similar to cancer centers, the Somnology and Sleep Medicine Centers of Excellence would act as local, regional, and national resources for the scientific community and the community at large. This will require coordination among all participating centers. Although online technologies greatly enhance the nearly instantaneous sharing of ideas across the nation and globally, the research network envisioned by the committee would involve not only a strong virtual component but also a structured plan for periodic and regular meetings and workshops to set priorities and strengthen interactions.

The committee strongly believes that the somnology and sleep medicine field is now sufficiently mature for the development of a National Somnology and Sleep Medicine Research Network and could successfully compete for network funding from the NHLBI and other members of the Trans-NIH Sleep Research Coordinating Committee that have substantial commitments to somnology and sleep disorders research. Individual Somnology and Sleep Medicine Centers of Excellence could compose the cornerstone of this network, and institutions that do not have sufficient scope and size to successfully compete for a Somnology and Sleep Medicine Center of Excellence would be active affiliate members of this network. The committee envisions a sustained network for somnology and sleep medicine in the United States that would facilitate public education, career development opportunities, translational research, and implementation of multi-center clinical trials.

The process of developing components of the National Somnology and Sleep Medicine Research Network can draw on the experiences of several such networks that already exist, but with more focused objectives, such as the aforementioned National Cancer Institute centers. The NHLBI currently sponsors 12 networks. The National Institute of Child Health and Human Development sponsors the National Center for Medical Rehabilitation Research regional research networks. Each network is coordinated and administered out of one academic institution, which coordinates the efforts of institutions that are affiliated with the network. The leading coordinating institutions are structured to facilitate major collaborations among affiliated institutions, with the potential to connect with researchers from other facilities within the region. They support multidisciplinary research cores, information transfer, and pilot projects with the goal of facilitating ongoing projects and stimulating the development of future research activities in medical rehabilitation (NCMRR, 2005).

Another example of a regional network is the Muscular Dystrophy Cooperative Research Centers. Cosponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Neurological Disorders and Stroke, the National Institute of Child Health and Human Development, as well as the Muscular Dystrophy Association, these centers work collaboratively on both basic and clinical research projects. Each center has one or more core facility to support them and must also make core resources or services available to the national muscular dystrophy research community.

The National Somnology and Sleep Medicine Research Network envisioned by the committee would be structured to facilitate and require active involvement of the participants and substantive interactions between basic and clinical researchers. As will be described in detail in Chapter 9, the committee calls on new and existing academic programs in somnology and sleep medicine to be organized to meet the criteria of three types of interdis-

ciplinary sleep programs—Type I, Type II, or Type III. A Type I clinical interdisciplinary sleep program is designed to provide optimal interdisciplinary clinical care for individuals who suffer sleep loss or sleep disorders. Although not consisting of large research components, a Type I program should have a data collection and management system that provides clinical data to a coordinating center within the network. A Type II training and research interdisciplinary sleep program includes the characteristics of a Type I program, but in addition is designed to provide optimal education, training, and research in somnology and sleep medicine. A Type III regional interdisciplinary sleep program coordinator includes the characteristics of Type I and II programs; however, a Type III program is designed to serve as a regional comprehensive center and coordinator for education, training, basic research, and clinical research in somnology and sleep medicine within the National Somnology and Sleep Medicine Research Network. The Committee also envisions that all Type I and II programs would be affiliate members of the National Somnology and Sleep Medicine Network.

Although there are only a limited number of academic institutions that currently have the capacity to be a Type III regional interdisciplinary sleep program, this should not delay the establishment of the research network. Initially the network could consist of a limited number of programs. The network would benefit greatly from cultural, ethnic, and environmental diversity. Therefore, a long-range goal should be to have 8 to 10 geographically distributed regional coordinating centers.

In summary, the National Somnology and Sleep Medicine Research Network should do the following:

- Coordinate and support the current cadre of basic and clinical researchers.
- Train new investigators and fellows through local and remote mentoring programs.
- Provide core facilities for basic research.
- Support multisite clinical research in children, adolescents, adults, and elderly people.
- Create and support virtual networking centers to facilitate the sharing of data and resources online and enhance collaborations with researchers not working in research centers.
- Create a data coordinating center that includes an Internet-based clearing house for the publication of all data produced in cooperation with the research and clinical network.
- Work with the CDC to integrate and support surveillance and population-based research.
- Create and coordinate public health education campaigns.

Efforts to develop a National Somnology and Sleep Medicine Research and Clinical Network are consistent with many of the goals of the NIH Roadmap (NIH, 2006b), including an emphasis on translational research that results in clinically useful therapies and a need for multidisciplinary efforts to be used to address this complex medical condition.

Recommendation 8.2: The National Institutes of Health should establish a National Somnology and Sleep Medicine Research Network.

The National Center on Sleep Disorders Research, in collaboration with the Trans-NIH Sleep Research Coordination Committee, should establish a National Somnology and Sleep Medicine Research Network. Type III regional interdisciplinary sleep programs designated by the National Institutes of Health would act as regional centers working with basic research laboratories and sleep cores at NIH-designated clinical translational research centers. It is envisioned that the networks would do the following:

- Coordinate and support the current and future cadre of basic and clinical researchers.
- Train new investigators and fellows.
- Provide core capabilities for basic, clinical, and translational research.
- Support multisite clinical research in children, adolescents, adults, and elderly.
- Create and support virtual networking centers to facilitate the standardization and sharing of data and resources online and enhance collaborations with researchers not working in research centers.
- Create a data coordinating center that includes an Internet-based clearing house for the publication of all data produced in cooperation with the research and clinical network.
- Together with the Agency for Healthcare Research and Quality develop standards for research, outcomes, and clinical practice.
- Work with the Centers for Disease Control and Prevention to integrate and support surveillance and population-based research.

Establish Sleep Laboratories in the NIH Clinical Research Program

As described in the 2003 research plan, “[t]he role of sleep disturbances and sleep disorders in the morbidity of most chronic conditions is understudied . . . [and] poorly understood” (NHLBI, 2003). The report further went on to call for greater study of the “bidirectional relationship between

sleep processes and disease development, progression, and morbidity.” Given these priorities, it is of note that the intramural clinical research program at the NIH does not have a sleep laboratory. Consequently, many experimental sleep therapies and the relationship between sleep processes and disease development are not being examined. If there is adequate investment in extramural sleep-related programs, the field can continue to make great strides; therefore, the committee does not support use of limited resources to invest in an intramural somnology and sleep disorders research program. However, because appropriate sleep patterns constitute one of the basic tenets of health, the committee strongly urges the NIH intramural clinical research program to ascertain the need for potentially establishing a sleep study laboratory so that evaluation of sleep may be integrated into ongoing relevant clinical research protocols at NIH.

Recommendation 8.3: The National Institutes of Health should ascertain the need for a transdisciplinary sleep laboratory that would serve as a core resource in its intramural clinical research program.

The director of the National Institutes of Health Intramural Research Program should ascertain the need for a transdisciplinary sleep laboratory within the intramural clinical research program that would serve as a core resource for the community of intramural clinical investigators across all institutes.

REFERENCES

- AASM (American Academy of Sleep Medicine). 2005. *The International Classification of Sleep Disorders*. Westchester, IL: AASM.
- Alvarez GG, Ayas NT. 2004. The impact of daily sleep duration on health: A review of the literature. *Progress in Cardiovascular Nursing* 19(2):56–59.
- Amiel J, Laudier B, Attie-Bitach T, Trang H, de Pontual L, Gener B, Trochet D, Etchevers H, Ray P, Simonneau M, Vekemans M, Munnich A, Gaultier C, Lyonnet S. 2003. Polyalanine expansion and frameshift mutations of the paired-like homeobox gene *PHOX2B* in congenital central hypoventilation syndrome. *Nature Genetics* 33(4):459–461.
- Amin RS, Kimball TR, Kalra M, Jeffries JL, Carroll JL, Bean JA, Witt SA, Glascock BJ, Daniels SR. 2005. Left ventricular function in children with sleep-disordered breathing. *American Journal of Cardiology* 95(6):801–804.
- Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. 1991. Sleep-disordered breathing in community-dwelling elderly. *Sleep* 14(6):486–495.
- Ancoli-Israel S, Klauber MR, Stepnowsky C, Estline E, Chinn A, Fell R. 1995. Sleep-disordered breathing in African-American elderly. *American Journal of Respiratory and Critical Care Medicine* 152(6 Pt 1):1946–1949.
- Babu AR, Herdegen J, Fogelfeld L, Shott S, Mazzone T. 2005. Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea. *Archives of Internal Medicine* 165(4):447–452.

- Bader G, Gillberg C, Johnson M, Kadesjö B, Rasmussen P. 2003. Activity and sleep in children with ADHD. *Sleep* 26:A136.
- Barger LK, Cade BE, Ayas NT, Cronin JW, Rosner B, Speizer FE, Czeisler CA, Harvard Work Hours HaS Group. 2005. Extended work shifts and the risk of motor vehicle crashes among interns. *New England Journal of Medicine* 352(2):125–134.
- Boggild H, Knutsson A. 1999. Shift work, risk factors and cardiovascular disease. *Scandinavian Journal of Work Environment Health* 25(2):85–99.
- Brown SA, Fleury-Olela F, Nagoshi E, Hauser C, Juge C, Meier CA, Chicheportiche R, Dayer JM, Albrecht U, Schibler U. 2005. The period length of fibroblast circadian gene expression varies widely among human individuals. *PLoS Biology* 3(10):e338.
- Buxbaum SG, Elston RC, Tishler PV, Redline S. 2002. Genetics of the apnea hypopnea index in Caucasians and African Americans: I. Segregation analysis. *Genetic Epidemiology* 22(3):243–253.
- Carskadon MA, Acebo C, Jenni OG. 2004. Regulation of adolescent sleep: Implications for behavior. *Annals of the New York Academy of Science* 1021:276–291.
- Cavallo A, Mallory ML, Association of Medical School Pediatric Department Chairs Inc. 2004. Sleep deprivation, residency training, and ACGME rules: Practical guidelines. *Journal of Pediatrics* 145(6):717–718.
- Cizza G, Skarulis M, Mignot E. 2005. A link between short sleep and obesity: Building the evidence for causation. *Sleep* 28(10):1217–1220.
- Czeisler CA, Walsh JK, Roth T, Hughes RJ, Wright KP, Kingsbury L, Arora S, Schwartz JR, Niebler GE, Dinges DF. 2005. Modafinil for excessive sleepiness associated with shift-work sleep disorder. *New England Journal of Medicine* 353(5):476–486.
- de la Eva RC, Baur LA, Donaghue KC, Waters KA. 2002. Metabolic correlates with obstructive sleep apnea in obese subjects. *Journal of Pediatrics* 140(6):654–659.
- Dolan-Sewell RT, Riley WT, Hunt CE. 2005. NIH State-of-the-Science Conference on Chronic Insomnia. *Journal of Clinical Sleep Medicine* 1(4):335–336.
- Fregosi RF, Quan SF, Kaemingk KL, Morgan WJ, Goodwin JL, Cabrera R, Gmitro A. 2003. Sleep-disordered breathing, pharyngeal size and soft tissue anatomy in children. *Journal of Applied Physiology* 95(5):2030–2038.
- Gillette MU, Roth T, Kiley JP. 1999. NIH funding of sleep research: A prospective and retrospective view. *Sleep* 22(7):956–958.
- Gottlieb DJ, Chase C, Vezina RM, Heeren TC, Corwin MJ, Auerbach SH, Weese-Mayer DE, Lesko SM. 2004a. Sleep-disordered breathing symptoms are associated with poorer cognitive function in 5-year-old children. *Journal of Pediatrics* 145(4):458–464.
- Gottlieb DJ, DeStefano AL, Foley DJ, Mignot E, Redline S, Givelber RJ, Young T. 2004b. APOE $\epsilon 4$ is associated with obstructive sleep apnea/hypopnea: The Sleep Heart Health Study. *Neurology* 63(4):664–668.
- Gottlieb DJ, Punjabi NM, Newman AB, Resnick HE, Redline S, Baldwin CM, Nieto FJ. 2005. Association of sleep time with diabetes mellitus and impaired glucose tolerance. *Archives of Internal Medicine* 165(8):863–867.
- Gozal D, Burnside MM. 2004. Increased upper airway collapsibility in children with obstructive sleep apnea during wakefulness. *American Journal of Respiratory and Critical Care Medicine* 169(2):163–167.
- Gurubhagavatula I, Maislin G, Nkwuo JE, Pack AI. 2004. Occupational screening for obstructive sleep apnea in commercial drivers. *American Journal of Respiratory and Critical Care Medicine* 170(4):371–376.
- Harrington JM. 1994. Shift work and health—A critical review of the literature on working hours. *Annals of the Academy of Medicine, Singapore* 23(5):699–705.
- Harris GC, Wimmer M, Aston-Jones G. 2005. A role for lateral hypothalamic orexin neurons in reward seeking. *Nature* 437(7058):556–559.

- Harsch IA, Schahin SP, Radespiel-Troger M, Weintz O, Jahreiss H, Fuchs FS, Wiest GH, Hahn EG, Lohmann T, Konturek PC, Ficker JH. 2004. Continuous positive airway pressure treatment rapidly improves insulin sensitivity in patients with obstructive sleep apnea syndrome. *American Journal of Respiratory and Critical Care Medicine* 169(2):156–162.
- Howard ME, Desai AV, Grunstein RR, Hukins C, Armstrong JG, Joffe D, Swann P, Campbell DA, Pierce RJ. 2004. Sleepiness, sleep-disordered breathing, and accident risk factors in commercial vehicle drivers. *American Journal of Respiratory and Critical Care Medicine* 170(9):1014–1021.
- Landrigan CP, Rothschild JM, Cronin JW, Kaushal R, Burdick E, Katz JT, Lilly CM, Stone PH, Lockley SW, Bates DW, Czeisler CA. 2004. Effect of reducing interns' work hours on serious medical errors in intensive care units. *New England Journal of Medicine* 351(18):1838–1848.
- Larkin EK, Patel SR, Redline S, Mignot E, Elston RC, Hallmayer J. 2005a. Apolipoprotein E and obstructive sleep apnea: Evaluating whether a candidate gene explains a linkage peak. *Genetic Epidemiology* 30(2):101–110.
- Larkin EK, Rosen CL, Kirchner HL, Storfer-Isser A, Emancipator JL, Johnson NL, Zambito AM, Tracy RP, Jenny NS, Redline S. 2005b. Variation of C-reactive protein levels in adolescents: Association with sleep-disordered breathing and sleep duration. *Circulation* 111(15):1978–1984.
- Lavie L. 2003. Obstructive sleep apnoea syndrome—An oxidative stress disorder. *Sleep Medicine Reviews* 7(1):35–51.
- Lockley SW, Cronin JW, Evans EE, Cade BE, Lee CJ, Landrigan CP, Rothschild JM, Katz JT, Lilly CM, Stone PH, Aeschbach D, Czeisler CA, Harvard Work Hours HaS Group. 2004. Effect of reducing interns' weekly work hours on sleep and attentional failures. *New England Journal of Medicine* 351(18):1829–1837.
- Lyamin O, Pryaslova J, Lance V, Siegel J. 2005. Animal behaviour: Continuous activity in cetaceans after birth. *Nature* 435(7046):1177.
- Manconi M, Govoni V, De Vito A, Economou NT, Cesnik E, Casetta I, Mollica G, Ferini-Strambi L, Granieri E. 2004. Restless legs syndrome and pregnancy. *Neurology* 63(6):1065–1069.
- Marcus CL, Katz ES, Lutz J, Black CA, Galster P, Carson KA. 2005. Upper airway dynamic responses in children with the obstructive sleep apnea syndrome. *Pediatric Research* 57(1):99–107.
- Maret S, Franken P, Dauvilliers Y, Ghyselinck NB, Chambon P, Tafti M. 2005. Retinoic acid signaling affects cortical synchrony during sleep. *Science* 310(5745):111–113.
- Marin JM, Carrizo SJ, Vicente E, Agusti AG. 2005. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: An observational study. *Lancet* 365(9464):1046–1053.
- Mignot E, Chen W, Black J. 2003. On the value of measuring CSF hypocretin-1 in diagnosing narcolepsy. *Sleep* 26(6):646–649.
- Monk TH. 2005. Aging human circadian rhythms: Conventional wisdom may not always be right. *Journal of Biological Rhythms* 20(4):366–374.
- Morin CM. 2004. Cognitive-behavioral approaches to the treatment of insomnia. *Journal of Clinical Psychiatry* 65(suppl 16):33–40.
- NCI (National Cancer Institute). 2004. *The Cancer Centers Branch of the National Cancer Institute: Policies and Guidelines Relating to the Cancer Center Support Grant*. [Online]. Available: http://www3.cancer.gov/cancercenters/CCSG_Guide12_04.pdf [accessed December 19, 2005].
- NCMRR (National Center for Medical Rehabilitation Research). 2005. *NCMRR Research Networks*. [Online]. Available: <http://www.nichd.nih.gov/about/ncmrr/networks.htm> [accessed December 19, 2005].

- NHLBI (National Heart, Lung, and Blood Institute). 1996. *National Sleep Disorders Research Plan, 1996*. Bethesda, MD: National Institutes of Health.
- NHLBI. 2003. *National Sleep Disorders Research Plan, 2003*. Bethesda, MD: National Institutes of Health.
- NIH (National Institutes of Health). 2004. *Program Announcement: PA-05-046*. [Online]. Available: <http://grants.nih.gov/grants/guide/pa-files/pa-05-046.html> [accessed March 6, 2006].
- NIH. 2005. *Request For Applications: RFA-HL-06-003*. [Online]. Available: <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-06-003.html> [accessed March 6, 2006].
- NIH 2006a. *Program Announcement PAR-05-144: Developing Centers for Innovation in Services and Intervention Research (DCISIR)*. [Online]. Available: <http://grants.nih.gov/grants/guide/pa-files/PAR-05-144.html> [accessed January 27, 2006].
- NIH. 2006b. *Request For Applications: RFA-RM-06-002*. [Online]. Available: <http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-06-002.html> [accessed February 6, 2006].
- NIMH (National Institute of Mental Health). 2006. *Program Announcement: PAR-02-123*. [Online]. Available: <http://grants.nih.gov/grants/guide/pa-files/PAR-02-123.html> [accessed January 27, 2006].
- Nishino S, Kanbayashi T. 2005. Symptomatic narcolepsy, cataplexy and hypersomnia, and their implications in the hypothalamic hypocretin/orexin system. *Sleep Medicine Reviews* 9(4):269–310.
- Nozinger EA, Buysse DJ, Germain A, Price JC, Miewald JM, Kupfer DJ. 2004. Functional neuroimaging evidence for hyperarousal in insomnia. *American Journal of Psychiatry* 161(11):2126–2128.
- Nowbar S, Burkart KM, Gonzales R, Fedorowicz A, Gozansky WS, Gaudio JC, Taylor MR, Zwillich CW. 2004. Obesity-associated hypoventilation in hospitalized patients: Prevalence, effects, and outcome. *American Journal of Medicine* 116(1):1–7.
- Owens JA, Rosen CL, Mindell JA. 2003. Medication use in the treatment of pediatric insomnia: Results of a survey of community-based pediatricians. *Pediatrics* 111(5 Pt 1):e628–e635.
- Palmer LJ, Buxbaum SG, Larkin E, Patel SR, Elston RC, Tishler PV, Redline S. 2003. A whole-genome scan for obstructive sleep apnea and obesity. *American Journal of Human Genetics* 72(2):340–350.
- Palmer LJ, Buxbaum SG, Larkin EK, Patel SR, Elston RC, Tishler PV, Redline S. 2004. Whole genome scan for obstructive sleep apnea and obesity in African-American families. *American Journal of Respiratory and Critical Care Medicine* 169(12):1314–1321.
- Petersen A, Gil J, Maat-Schieman ML, Bjorkqvist M, Tanila H, Araujo IM, Smith R, Popovic N, Wierup N, Norlen P, Li JY, Roos RA, Sundler F, Mulder H, Brundin P. 2005. Orexin loss in Huntington's disease. *Human Molecular Genetics* 14(1):39–47.
- Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE, Sleep Heart Health Study Investigators. 2004. Sleep-disordered breathing, glucose intolerance, and insulin resistance: The Sleep Heart Health Study. *American Journal of Epidemiology* 160(6):521–530.
- Rattenborg NC, Mandt BH, Obermeyer WH, Winsauer PJ, Huber R, Wikelski M, Benca RM. 2004. Migratory sleeplessness in the white-crowned sparrow (*Zonotrichia leucophrys gambelii*). *PLoS Biology* 2(7):E212.
- Rosen CL, Larkin EK, Kirchner HL, Emancipator JL, Bivins SF, Surovec SA, Martin RJ, Redline S. 2003. Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: Association with race and prematurity. *Journal of Pediatrics* 142(4):383–389.
- Rosen CL, Storfer-Isser A, Taylor HG, Kirchner HL, Emancipator JL, Redline S. 2004. Increased behavioral morbidity in school-aged children with sleep-disordered breathing. *Pediatrics* 114(6):1640–1648.
- Roth T, Roehrs T. 2003. Insomnia: Epidemiology, characteristics, and consequences. *Clinical Cornerstone* 5(3):5–15.

- Row BW, Liu R, Xu W, Kheirandish L, Gozal D. 2003. Intermittent hypoxia is associated with oxidative stress and spatial learning deficits in the rat. *American Journal of Respiratory and Critical Care Medicine* 167(11):1548–1553.
- Rye DB. 2004. The two faces of Eve: Dopamine's modulation of wakefulness and sleep. *Neurology* 63(8 Suppl 3):S2–S7.
- Saper CB, Scammell TE, Lu J. 2005. Hypothalamic regulation of sleep and circadian rhythms. *Nature* 437(7063):1257–1263.
- Singh M, Drake C, Roehrs T, Koshorek G, Roth T. 2005. The prevalence of SOREMPs in the general population. *Sleep* 28(Abstract Suppl):A221.
- Spiegel K, Tasali E, Penev P, Van Cauter E. 2004. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Annals of Internal Medicine* 141(11):846–850.
- Tafti M, Petit B, Chollet D, Neidhart E, de Bilbao F, Kiss JZ, Wood PA, Franken P. 2003. Deficiency in short-chain fatty acid beta-oxidation affects theta oscillations during sleep. *Nature Genetics* 34(3):320–325.
- Taheri S, Lin L, Austin D, Young T, Mignot E. 2004. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Medicine* 1(3):210–217.
- Tauman R, Ivanenko A, O'Brien LM, Gozal D. 2004. Plasma C-reactive protein levels among children with sleep-disordered breathing. *Pediatrics* 113(6):e564–e569.
- Trenkwalder C, Paulus W, Walters AS. 2005. The restless legs syndrome. *Lancet Neurology* 4(8):465–475.
- Turek FW, Joshu C, Kohsaka A, Lin E, Ivanova G, McDearmon E, Laposky A, Losee-Olson S, Easton A, Jensen DR, Eckel RH, Takahashi JS, Bass J. 2005. Obesity and metabolic syndrome in circadian *Clock* mutant mice. *Science* 308(5724):1043–1045.
- U.S. Congress, Senate. 1993. *National Institutes of Health Revitalization Act of 1993; bill to establish a National Center on Sleep Disorders Research within the National Heart, Lung, and Blood Institute*. 103rd Cong., S.104:285b–287.
- Veasey SC, Davis CW, Fenik P, Zhan G, Hsu YJ, Pratico D, Gow A. 2004a. Long-term intermittent hypoxia in mice: Protracted hypersomnolence with oxidative injury to sleep-wake brain regions. *Sleep* 27(2):194–201.
- Veasey SC, Zhan G, Fenik P, Pratico D. 2004b. Long-term intermittent hypoxia: Reduced excitatory hypoglossal nerve output. *American Journal of Respiratory and Critical Care Medicine* 170(6):665–672.
- Weese-Mayer DE, Berry-Kravis EM, Zhou L, Maher BS, Silvestri JM, Curran ME, Marazita ML. 2003. Idiopathic congenital central hypoventilation syndrome: Analysis of genes pertinent to early autonomic nervous system embryologic development and identification of mutations in *PHOX2b*. *American Journal of Medical Genetics: Part A* 123(3):267–278.
- Xu Y, Padiath QS, Shapiro RE, Jones CR, Wu SC, Saigoh N, Saigoh K, Ptacek LJ, Fu YH. 2005. Functional consequences of a *CK1delta* mutation causing familial advanced sleep phase syndrome. *Nature* 434(7033):640–644.
- Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. 2005. Obstructive sleep apnea as a risk factor for stroke and death. *New England Journal of Medicine* 353(19):2034–2041.
- Yamazaki S, Numano R, Abe M, Hida A, Takahashi R, Ueda M, Block GD, Sakaki Y, Menaker M, Tei H. 2000. Resetting central and peripheral circadian oscillators in transgenic rats. *Science* 288(5466):682–685.
- Yokoe T, Minoguchi K, Matsuo H, Oda N, Minoguchi H, Yoshino G, Hirano T, Adachi M. 2003. Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. *Circulation* 107(8):1129–1134.

- Yoo SH, Yamazaki S, Lowrey PL, Shimomura K, Ko CH, Buhr ED, Sieppka SM, Hong HK, Oh WJ, Yoo OJ, Menaker M, Takahashi JS. 2004. PERIOD2::LUCIFERASE real-time reporting of circadian dynamics reveals persistent circadian oscillations in mouse peripheral tissues. *Proceedings of the National Academy of Sciences of the United States of America* 101(15):5339–5346.
- Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. 1993. The occurrence of sleep-disordered breathing among middle-aged adults. *New England Journal of Medicine* 328(17):1230–1235.

9

Building Sleep Programs in Academic Health Centers

CHAPTER SUMMARY *New organizational structures for interdisciplinary sleep programs in academic health centers are necessary. This chapter makes the case for why interdisciplinary sleep programs are needed nationwide. It then offers a framework for establishing academic somnology and sleep medicine programs. Without being prescriptive, the chapter discusses operating principles gleaned from interdisciplinary somnology and sleep medicine programs that have flourished, as well as from others that have struggled. Finally, the chapter unveils the committee's recommendation for a three-tier structure that ensures all academic health centers provide adequate interdisciplinary clinical care, with subsequent tiers also emphasizing training and research components. If these components and guiding principles are followed, interdisciplinary sleep programs can thrive, whether as a freestanding department or as a program within an existing department or division. Although not a trivial undertaking, it is necessary that all academic health centers strive to develop or transform their current sleep activities into interdisciplinary sleep programs. Some academic health centers are close to, or already have, achieved strong clinical programs. Once a sleep program is established, whether multidimensional or not, it can generate higher revenues than costs, according to a fiscal analysis presented in this chapter. To ensure improved care and scientific advances, the committee recommends clinical accreditation standards be updated to address patient care needs.*

Building sleep programs at academic health centers is not a matter of bricks and mortar. It is a matter of crumbling the organizational walls that separate a variety of traditional scientific and medical disciplines to function more appropriately to meet patient care needs and to facilitate research and training. In this chapter, the committee lays out a vision for each of the nation's 125 academic health centers to formally establish an interdisciplinary somnology and sleep medicine program. Building sleep programs nationwide will strengthen Somnology and Sleep Medicine as a recognized medical specialty. There is too much at stake—a large patient population, high levels of underdiagnosis, and high public health toll—for inaction.

RATIONALE FOR SLEEP PROGRAMS IN ACADEMIC HEALTH CENTERS

The rationale for sleep programs has been presented throughout this report. This section of the chapter recapitulates those arguments concerning the magnitude of the public health problem and the lack of appropriate education at every level of academic instruction. It also answers the specific question—why is a sleep program optimally interdisciplinary?

Public Health Burden Is High

Chronic sleep loss and sleep disorders are serious and common problems, affecting an estimated 50 to 70 million Americans (NHLBI, 2003). These conditions have a bearing upon nearly every facet of public health—morbidity, mortality, productivity, accidents and injuries, quality of life, family well-being, and health care utilization. Earlier chapters of this report documented the prevalence of sleep problems and their health consequences. Sleep loss and sleep-disordered breathing, for example, are associated with obesity, diabetes, hypertension, cardiovascular disease, and stroke (Chapter 3).

Nearly all types of sleep problems affect personal as well as public health (Chapter 4). The foremost symptom of sleep loss and most sleep disorders—daytime sleepiness—affects performance and cognition. When these functions are perturbed, whether at work, in school, or in the community, serious consequences can ensue. One of the most serious comes in the form of motor vehicle injuries. More broadly, the annual direct and indirect costs of sleep problems reach well beyond \$100 billion (Chapter 4).

Most Patients Remain Undiagnosed and Untreated

Most individuals with sleep disorders remain undiagnosed and thus untreated. Two large epidemiological studies, each with thousands of subjects, found that the vast majority, up to 90 percent, of individuals with

sleep-disordered breathing had not been diagnosed (Young et al., 1997; Kapur et al., 2002). Narcolepsy and insomnia are also infrequently detected (Benca, 2005; Singh et al., 2005). All of the findings reported above are consistent with surveys indicating that primary care physicians infrequently ask questions about sleep problems (Chung et al., 2001; Reuveni et al., 2004).

Patients with Sleep Loss and Sleep Disorders Require Long-Term Care and Chronic Disease Management

Sleep disorders are chronic conditions with complex treatments. They are frequently comorbid with other sleep disorders, as well as other complex conditions (e.g., cardiovascular disease, depression, and diabetes) (Chapter 3). Sleep disorders also are dynamic, meaning that the underlying condition or its treatment changes with age and onset of new comorbidities.

Despite the importance of early recognition and treatment, the primary focus of most existing sleep centers is on diagnosis rather than on comprehensive management of sleep loss and sleep disorders as chronic conditions. The narrow focus of sleep centers may largely be the unintended result of accreditation criteria, which emphasize diagnostic standards, as explained later, as well as a result of reimbursement, which is for diagnostic testing.

There are numerous reasons for a paradigm shift to chronic disease management. Proper treatment for most sleep disorders—as for other chronic diseases such as congestive heart failure, diabetes, asthma, and depression—requires a period of time for fine-tuning, extended follow-up, and lifestyle changes. Sleep disorders cannot be adequately treated in a single visit.

The need for chronic care management is even more pressing for the many patients (probably up to 30 percent) with combined sleep pathologies. These patients are difficult to manage without multiple clinicians being involved. For example, 20 to 50 percent of narcoleptics have obstructive sleep apnea (OSA); 40 percent of narcoleptics have insomnia; 40 percent of narcoleptics have periodic leg movements disorder (Baker et al., 1986; Cherniack, 2005; Chung, 2005). Residual daytime sleepiness is common in patients with sleep apnea adequately treated with continuous positive airway pressure (CPAP); it may require additional pharmacotherapy. Similarly, a large portion of patients with sleep apnea have insomnia and vice versa. Insomnia plus sleep apnea is a difficult combination, as it makes it more challenging for patients to tolerate CPAP and thus increases the likelihood of failure if the combination is not addressed.

Sleep disorders are also common in patients with various medical and psychiatric conditions. For example, increased sleep apnea is found in obese subjects with or without the metabolic syndrome and in patients with stroke or various neurodegenerative disorders. Restless legs syndrome can occur in

the context of iron deficiency, renal failure, and pregnancy. Rapid-eye-movement (REM) behavior disorder is often an antecedent of Parkinson's disease and Lewy body disease. Hypersomnia is a common symptom in Parkinson's disease, depression, and various neurological conditions. Similarly, insomnia can occur in the context of various medical and psychiatric conditions and is associated with depression. These patients often require coordinated care across disciplines. As will be described below, interdisciplinary sleep programs provide the best structure to facilitate this type of care.

Inadequate Numbers of Training and Research Programs

Training of health professionals seldom deals with sleep hygiene, sleep loss, and sleep disorders (Chapters 5 and 7). Although there have been some improvements, challenges lie ahead for training of medical, nursing, and pharmacy students. Research opportunities for medical residents, subspecialty residents, and doctoral and postdoctoral researchers are also limited. Most sleep researchers are clustered in a handful of institutions, according to the grants analysis presented in Chapter 7. Because mentoring is critical to success in clinical or basic research, the concentration of mentors at so few institutions leaves students elsewhere with few opportunities to successfully enter the field, thereby constricting the pipeline of new clinicians and researchers.

Large Body of Knowledge

Given the limited number of sleep experts nationwide and their clustering in a handful of institutions, is there a sufficient knowledge base and need to justify creation of an interdisciplinary somnology and sleep medicine program at each of the nation's academic health centers? The simple answer is yes. Over the last 25 years, the field has grown to the point that a large base of knowledge now exists regarding diagnosis and treatment. Several recent milestones for the field attest to the achievement of a critical mass of knowledge. Sleep medicine is a medical subspecialty now recognized by the American Board of Medical Specialties. The Accreditation Council for Graduate Medical Education (ACGME) now accredits fellowship training programs. Numerous educational resources, including curriculum, are available from the American Academy of Sleep Medicine. The standard 1,500-page textbook, *Principles and Practice of Sleep Medicine*, is in its fourth edition. There is also a vibrant body of research, described in previous chapters, on the basic science of sleep and sleep disorders. The number of recipients of National Institutes of Health (NIH) R01 grants in sleep has risen from 100 to 253 over the last 10 years (Chapter 8).

Why Is Somnology and Sleep Medicine Program Optimally Interdisciplinary?

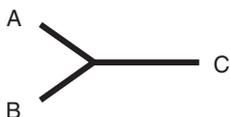
Medicine has historically drawn strength from compartmentalizing into distinct specialties and subspecialties. But sleep medicine is not an ordinary subspecialty; its purview spans multiple organ systems. Consequently, complications that arise as a result of sleep loss and sleep disorders require attention from health care professionals in many disciplines. Further, sleep cycles and perturbations exert physiological effects. The major circadian rhythm that originates in the brain influences body temperature, heart rate, muscle tone, and the secretion of hormones. There are also circadian clocks in the heart and other organs. Beyond maintaining proper health and normal cognitive and motor function, sleep is required for survival (Rechtschaffen et al., 1989). Disturbance of sleep or loss of sleep has widespread metabolic implications (Chapter 2). Finally, the scientific study of sleep loss and sleep disorders integrates the efforts of many disciplines, including but not limited to neuroscience, epidemiology, molecular and cellular biology, and genetics.

Thus, by its very nature, the field is at the interface of many medical and scientific disciplines. Therefore, it is not surprising that board certification in sleep medicine is under the auspices of four different medical boards—the American Boards of Internal Medicine, Pediatrics, Otolaryngology, and Psychiatry and Neurology.

To harness the needed specialties, sleep programs must be multidisciplinary. But being multidisciplinary is not sufficient. A true interdisciplinary program is an orientation, approach, or philosophy that seeks to go beyond the sum of the parts to build a new enterprise (Figure 9-1). It is not necessary for sleep medicine to be housed in a stand-alone department or division. Many interdisciplinary sleep programs thrive in a department (see below). However, sleep programs that are restricted to a single department that does not allow for interdisciplinary treatment and care tend to struggle. This is partly because they fail to provide a sense of identity; they lack a career path for faculty, which in turn, makes it difficult to recruit students and additional faculty—the very ingredients needed to establish and rejuvenate a field. Further, fragmented programs lack the collaborative spirit necessary for excellence in clinical care, training, and research.

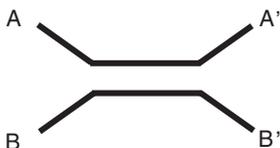
The field of somnology and sleep medicine is an excellent example of an interdisciplinary field because it strives to integrate ideas, tools, and perspectives from several disciplines in order to advance understanding beyond the scope of a single discipline or field of research practice. The field is being forged from existing fields of cardiology, dentistry, endocrinology, geriatrics, neurology, neuropsychopharmacology, neuroscience, nursing, otolaryngology, pediatrics, psychiatry, psychology, and pulmonology (Box 9-1). Although

A) Interdisciplinary



Joined together to work on a common question or problem. Interaction may forge a new research field or discipline.

B) Multidisciplinary



Disciplines joined together to work on a common question or problem, split apart when work is complete, having likely gained new knowledge, insight, strategies from other disciplines.

FIGURE 9-1 Interdisciplinary and multidisciplinary research.
SOURCE: NAS (2004).

not all of these disciplines are essential for starting a sleep program, each enriches the sleep field in transcendent ways. Two of the most advanced and successful sleep programs, at Harvard University and the University of Pennsylvania, attest to the productivity and vibrancy of an interdisciplinary approach. The success of the program at the University of Pennsylvania also demonstrates that the success of an interdisciplinary sleep program is not dependent on it being its own stand-alone department.

Many types of health professionals are needed to guide the chronic management of sleep disorders. Individuals with sleep loss and sleep disorders have a multitude of health-related problems that require attention from a number of medical disciplines. However, given the limited number of certified health care professionals in sleep medicine and depending on the size and structure of an interdisciplinary sleep program, an individual often may need to be referred to a specialist in another department who may not be certified in sleep medicine. These physicians come from a variety of medical specialties, including internal medicine, pediatrics, otolaryngology, pulmonology, neurology, and psychiatry. Psychologists are essential in behavioral management of sleep disorders.

Nurses and nurse practitioners also play an important role in patient support, patient teaching (especially in sleep hygiene and use of CPAP), follow-up, and promoting adherence to prescribed medical therapies (Epstein and Bootzin, 2002; Lee et al., 2004b). For example, in one of the

BOX 9-1
**Examples of Interdisciplinary Approaches
to Somnology and Sleep Medicine**

Several major accomplishments of somnology and sleep medicine have critically depended on the insights and perspectives of disparate disciplines:

Cardiology

Contributions of cardiology and large cohorts such as the Framingham study led to the Sleep Heart Health Study. This large cohort study has shown that sleep apnea is a risk factor for hypertension, cardiovascular disease, and insulin resistance (Nieto et al., 2000; Shahar et al., 2001; Punjabi et al., 2004).

Endocrinology

Cumulative sleep loss led to reduced leptin and increased ghrelin and hence increased appetite (Spiegel et al., 2004; Taheri et al., 2004). This led to the hypothesis that a hormonally mediated increase in appetite may help to explain why short sleep is a risk factor for obesity.

Pulmonary

Pulmonologists, with their knowledge of pulmonary physiology and ventilators, led the development of nasal CPAP, the most efficacious and common treatment for OSA (Sullivan et al., 1981).

Neurobiology and Genetics

Contributions of neurobiologists led to the demonstration that the rest period in the fruit fly (*Drosophila*) is analogous to mammalian sleep (Shaw et al., 2000; Hendricks et al., 2000). This provides a powerful new genetic model to study sleep mechanisms.

Nursing

Nursing's focus on quality of life led to development of the Functional Outcomes of Sleepiness Questionnaire (Weaver et al., 1997). This instrument, which measures functional capacity in relation to sleep, is now used in clinical trials.

few studies of its kind, group education sessions with a pulmonary nurse practitioner were found to enhance CPAP compliance over a 2-year period (Likar et al., 1997). Other nursing interventions, such as appropriately timed exercise, relaxation, and meditation, have also been shown to have beneficial effects on sleep in patients with chronic illnesses such as cancer and those in the acute care setting (Davidson et al., 2001; Mock et al., 2001; Richards et al., 2003; Allison et al., 2004). The role that poor sleep plays in enhancing other symptoms such as depression, fatigue, and pain is also

receiving increased attention by nurse clinicians and researchers in an attempt to improve overall symptom management (Miaskowski and Lee, 1999; Lee et al., 2004a; Miaskowski, 2004; Parker et al., 2005).

Despite its promise, the field, like any enterprise that strives to cut across traditional disciplines, is fragile—even in the most supportive environments (NAS, 2004). Sleep clinicians or researchers often face daunting obstacles and disincentives, most of which arise from the customs and practices of individual academic departments. Those obstacles are discussed later in this chapter.

CONSTRAINTS FACING INTERDISCIPLINARY SLEEP PROGRAMS

Many of the most promising new lines of academic pursuit fall outside of traditional disciplines (Ehrenberg and Epifantseva, 2001). Yet interdisciplinary programs, even under the best of circumstances, face barriers and impediments within the confines of academic or research institutions (Ehrenberg et al., 2003; Lach and Schankerman, 2003). A recent National Academies report focusing on ways to facilitate interdisciplinary research was unambiguous about the difficulties confronting these programs, despite their promise. The report observed that, “Researchers interested in pursuing [interdisciplinary research] often face daunting obstacles and disincentives.” Some of these obstacles take the form of personal communication or culture barriers; others are related to the tradition in academic institutions of organizing research and teaching activities by discipline-based departments—a tradition that is commonly mirrored in funding organizations, professional societies, and journals (NAS, 2004). This is a generic problem, regardless of whether the interdisciplinary research program deals with nanotechnology or the perception of pain.

The problem of departmental silos permeates interdisciplinary programs within any setting: academic health centers, universities, national laboratories, or industry. The following section presents a series of constraints that together limit the achievement of interdisciplinary programs. These constraints were identified on the basis of an analysis of six sleep programs using methods from operations research that the committee commissioned (see below). Several of the other constraints described in the following sections stem from organizational structures that were established prior to the advent of interdisciplinary research: interdisciplinary programs challenge institutional reward systems; interdisciplinary requirements impose obstacles, different administrative jurisdictions, and lack of appropriately trained staff for sleep studies; and service demand outstrips service supply.

Different Administrative Jurisdictions

As a corollary of the interdisciplinary nature of sleep programs, another constraint is that the services offered by a sleep program often occur at different locations under different administrative jurisdictions. Coordinating all the different types of personnel, lines of authority, policy and procedures, and quality control measures across organizational boundaries is challenging. Who bears the costs and their alignment with benefits and the various revenue streams is neither obvious nor consistent.

Interdisciplinary Programs Challenge the Institutional Reward System

Most institutional reward systems are organized within traditional disciplines or academic departments. These are the units that control what most professionals covet: hiring capacity, tenure and promotion decisions, and space allocation. Interdisciplinary programs challenge this discipline-based reward system, as well as the culture accompanying each discipline (i.e., the customs and shared values that create group cohesion).

The National Academies report on interdisciplinary research conducted three surveys of different groups either working within or overseeing interdisciplinary programs: individual professionals, provosts, and attendees of a conference on interdisciplinary research. In all, some 500 people responded to the surveys (NAS, 2004). The report acknowledges that the samples were not random. But since these are the only surveys of their kind, it is worth noting that the overwhelming majority of respondents (70.7 percent) reported that there were impediments at their institution. The leading barriers identified by individual professionals and provosts: promotion criteria, budget control, control on use of indirect costs, compatibility with university's strategic plans, and space allocation (Figure 9-2).

Interdisciplinary Requirements Impose Obstacles

Interdisciplinary sleep programs, at a minimum, require multidisciplinary participation. As explained earlier, an interdisciplinary program moves beyond being multidisciplinary and is one in which multiple disciplines collaborate in a way that forges a new discipline or endeavor. Provision of clinical services in sleep medicine call upon professionals from internal medicine and its relevant subspecialties (e.g., pulmonology, cardiology, neurology, psychiatry, otolaryngology, pediatrics, and geriatrics) and other disciplines such as nursing, dentistry, and psychology. Research includes genetics, endocrinology, neuroscience, statistics, pharmacology, and epi-

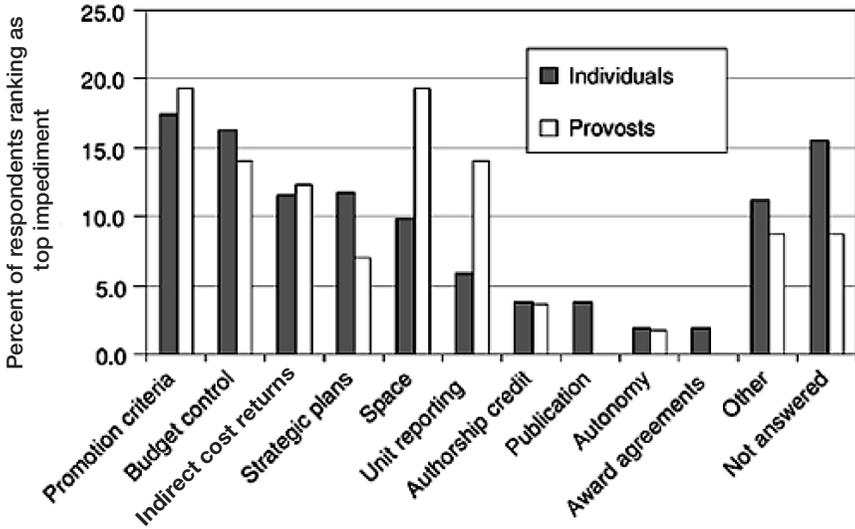


FIGURE 9-2 Barriers to interdisciplinary research.
SOURCE: NAS (2004).

miology. Similar issues exist in teaching undergraduate, graduate, and physicians in their residencies, fellowships, and postdoctoral work.

The unintended consequence is to produce barriers to interdisciplinary patient care, training, and research. Barriers include the length and depth of training in a single field necessary to develop scientists successful at competing for funds, the difficulty in forging a successful career path outside the single disciplinary structure, impediments to obtaining research funding for interdisciplinary research, and the perceived lack of outlets for the publication and dissemination of interdisciplinary research results.

Lack of Appropriately Trained Staff for Sleep Studies

By nearly universal consensus, one sleep technician can monitor at one time two uncomplicated diagnostic studies or one complicated study. Yet, the number of certified technicians nationally is inadequate to meet this need. As with any market in which the supply is less than demand, costs of certified technicians is rising faster than the average rate of inflation or the average rate of medical costs. This has two likely consequences: sleep programs are forced to provide on-the-job training for their technicians; and private-sector organizations are able to adjust their payment structures more readily than academic health centers. Thus, academic centers often provide training, but higher salaries in the private sector lure the experienced technologists. The

net consequence is that the lack of trained technicians can act as a serious structural impediment to developing interdisciplinary sleep programs.

Demand Outstrips Supply

Estimates suggest that 50 to 70 million Americans suffer from a chronic disorder of sleep and wakefulness (NHLBI, 2003). As discussed in detail in Chapter 6, the predicted number of individuals with sleep disorders greatly outstrips the ability to provide services using trained personnel (Tachibana et al., 2005). Although there are over 3,250 American Board of Sleep Medicine (ABSM) diplomats, inadequate staffing results in long wait time until next appointment. Analysis commissioned on behalf of the committee indicated that wait times could range by as much as 4 weeks to 4 months.

KEY COMPONENTS AND GUIDING PRINCIPLES FOR BUILDING SLEEP PROGRAMS

In this section, the committee offers guidance to academic health centers about the missions and roles of sleep programs. There is no single way to create or expand an interdisciplinary sleep program. The committee recognizes that every institution has established—often over many decades—its own policies, procedures, institutional organization, and lines of authority. The committee offers principles that can guide development of somnology and sleep medicine programs. For each of these key components and guiding principles, the committee draws on its experience with programs that have been successful, as well as those that have struggled. It also draws on the formidable barriers identified in the previous section. If these components and guiding principles are followed, interdisciplinary sleep programs can thrive, whether as a freestanding department or as a program within an existing department or division.

Key Components of Interdisciplinary Sleep Programs

Strong Linkages from Diagnostic Testing Centers to Comprehensive Care

Diagnostic sleep centers need to establish strong linkages with treatment providers. The emphasis of sleep centers may be too narrowly focused on diagnosis. The committee heard testimony and anecdotal reports that many patients, once tested, are lost to follow-up. Once diagnosed, severe sleep apnea, for instance, optimally should be followed up by a physician certified in sleep medicine. Less severe forms of apnea may warrant watching or referral to a dentist for preparation of dental devices, if a dental problem is etiologically related.

A Chronic Disease Management Model

Responding to the well-documented problem that most Americans with chronic diseases receive suboptimal care (IOM, 2000; 2001), Wagner and colleagues have developed and tested a model for improved management of chronic illness in the primary care setting. Components of the model have been demonstrated to lower health care costs or lower use of health care services (Bodenheimer et al., 2002). The model's six components are:

- community resources (e.g., exercise programs, senior centers, and self-help groups)
- health care organization (a provider organization and its relationships with purchasers, insurers, and other providers)
- self-management support (ways to help families acquire the skills and confidence to manage their chronic illnesses)
- delivery system design (structuring medical practice to create teams, including nonphysician personnel, for patient support and follow-up)
- decision support (access to specialists that does not necessarily require a specialty referral)
- clinical information systems (e.g., reminder systems, feedback to physicians, registries for planning patient care)

Education and Training

Few health professionals receive adequate training in somnology and sleep medicine, as summarized earlier in this chapter and considered in depth in Chapters 5 and 7. At a minimum, medical students need basic training in sleep disorders, as do pharmacy, public health, dentistry, and nursing students. This training should cover the public health burden of sleep loss and sleep disorders and the importance of diagnosis and treatment throughout the life span. Sleep disorders and sleep medicine should be covered in greater depth in residency and fellowship training programs in all primary care specialties, as well as specialties related to sleep (e.g., otolaryngology), but without formal ACGME-accredited sleep fellowship programs. Research training—for clinical fellows, as well as for graduate and postgraduate researchers—is a key component for more specialized sleep programs (Type II and III; see below).

Clinical, Basic, and Translational Research

The field, as an interdisciplinary enterprise, garners momentum from the many clinical and basic disciplines at its core. The translational opportunities inherent in the field were among the motivations behind the forma-

tion by the NIH, in 1986, of the Trans-NIH Sleep Research Coordinating Committee (Chapter 8). The coordination and integration of many scientific fields will maximize these efforts.

Participation in Proposed Research Network

The committee recommended in Chapter 8 the creation of a National Somnology and Sleep Medicine Research and Clinical Network. The purpose of the proposed network is to advance the field by providing a means to connect individual investigators, research programs, and research centers. The network would provide a resource for education, training, collaborations, core facilities, data coordination, and access to multisite clinical research trials. Most sleep programs could benefit greatly from participation in the proposed network. For the network to be successful, all participating programs should be required to submit research and clinical data to whatever joint projects the network undertakes. This concept parallels the structure of many existing networks supported by NIH, as noted in Chapter 8.

Guiding Principles of Interdisciplinary Sleep Programs

Leadership

Leadership, so easily recognizable but elusive to define, is the single greatest success factor in forming a new program. The most successful programs developed over the past two decades are largely traceable to the conviction, determination, and persistence of committed leaders. These programs have served as beacons to others, facilitating their establishment. In a survey of 186 principal investigators, the IOM and National Academies committee on interdisciplinary research asked, "If you could recommend one action that principal investigators could take that would best facilitate interdisciplinary research, what would that be?" The leading recommendation from this survey was to increase leadership support of team-forming activities (NAS, 2004).

Revenue Generation and Fiscal Independence

Established sleep programs can generate higher revenues than costs, according to the analysis that the committee commissioned. This has resulted in individual departments taking "ownership" of the sleep program, thereby limiting reinvestment potential. But this is a shortsighted strategy. As emphasized throughout this report, there is enormous opportunity both in terms of clinical service and research. Academic centers, which adopt budgeting strategies that offer individual incentives to work together, should

be better positioned to promote interdisciplinary research. Moreover, deans can facilitate interdisciplinary research by specifically giving chairpersons incentives for this type of activity. Such strategies give deans a very specific role in development of and support of somnology and sleep medicine as an interdisciplinary discipline.

Transparent Policies and Procedures

Sleep programs that are administered as divisions within individual departments may be at a disadvantage. They are not represented at the level of the school of medicine and hence may not be directly involved in strategic planning initiatives of the academic medical center. Further, the program competes for faculty positions in a structure that is not focused on development of interdisciplinary programs. On the other hand, entities that have medical-school-wide structures that support the interdisciplinary nature of sleep medicine have the converse—they are involved in strategic planning, there is financial transparency with budget authority, and they have the ability to advocate for faculty positions.

ORGANIZATIONAL AND FISCAL STRUCTURES FOR SUSTAINING OR EXPANDING A SLEEP PROGRAM

How can programs in somnology and sleep medicine be organized to sustain themselves and grow? This was the driving question behind an analysis the committee commissioned. The analysis focused on organization and fiscal structure of five interdisciplinary sleep programs—each with clinical, teaching, and research capacity. By studying programs with distinct organizational structures, the analysis sought to determine which were most conducive to sustaining or expanding their sleep program.

The analysis was undertaken using methods from operations research, a field that examines the impact of organizational structure on a program's capacity to achieve its mission. Operations research has shown that a program's success not only depends on leadership and quality of faculty and students, but also on its organization. It has identified organizational structure as being associated with success in producing doctorates (Ehrenberg and Epifantseva, 2001), acquiring grants (Ehrenberg et al., 2003), and developing patented technology (Luszki, 1958; Lach and Schankerman, 2001; 2003). This section of the chapter summarizes the specific questions, methods, and major findings of the commissioned paper. It is important to point out that the choice of programs was meant neither to be representative of all sleep programs, nor to cover the question of how to start a program de novo. Consequently, although the general findings are consistent,

any conclusions drawn from the analysis may be limited and may not transcend every medical center.

Specific Questions and Methodology

The analysis addresses three specific questions: (1) Can sleep programs generate revenue in excess of their costs? (2) Which revenue streams produce the largest net revenue available for program development? (3) What organizational structure maximizes control over resources for program development? Parametric analysis applying the principles of operations research was used to examine these three questions. Semistructured interviews were conducted at five academic sleep programs with varying organizational structures: Emory University, George Washington University, Stanford University, University Hospital of Cleveland, and University of Pennsylvania. The interviews dealt with the topics in Box 9-2. Financial data were obtained from each program, and direct observations were performed, including the provision of clinical services and the effect of teaching on patient throughput. Major priorities of the analysis were to develop an operational framework to categorize organizational structures, to delineate specific constraints affecting sleep programs, to identify major cost structures and major funding streams, and to develop a “business plan” for each major organizational variant most likely to sustain or expand its program.

Direct Costs

The analysis identified three major direct costs: clinical services, teaching, and research. Clinical services consist of obtaining a reliable clinical history from a patient, determining what studies to conduct and, based on findings, establishing a diagnosis and developing a treatment plan. Diagnostic sleep studies are constrained by the fact that a sleep technician simultaneously can run, at best, two studies. “Reading” of studies requires frequent technician and clinician “calibration” for quality assurance purposes. Most programs are able to generate approximately 30 readings a week per full-time equivalent. Incorrect staffing ratios (e.g., medical assistant to provider ratios lower than 2 to 1) often produce longer patient wait times, which negatively affect patient throughput. No-show rates typically increase beyond a 2-week “next appointment” wait time. The direct costs of performing a sleep study are rising rapidly, primarily as a result of personnel costs. The changes in direct service costs between 1994, 2000, and 2005 are depicted in Figure 9-3.

The programs in the study taught medical students, residents, doctoral students, sleep fellows, and postdoctoral fellows. Though many faculty

BOX 9-2
Areas Addressed in Semistructured Interviews

1. A description of the program's revenue stream(s)
 - a. Tests, including polysomnograms
 - b. Treatment protocols
 - c. Clinical consults
 - d. Other services
2. Approximate operating budget for:
 - a. Number of staff
 - i. Administrative
 - ii. Technical support
 - iii. Practitioners
 - b. Number of beds allocated to sleep
 - c. Equipment maintenance and upgrades
 - d. Training and continuing education
 - e. Basic and clinical research
 - f. The amount and source of discretionary funds controlled by the sleep center director
3. What percentage of the center's revenue goes to its parent department or division?
4. What percentage of the center's revenue goes to other departments through cost-sharing agreements?
5. What percentage of the center's operating budget does your sleep center receive from its parent department or division?
6. What are the challenges in working under the current system—does this create any barriers in care or service?
7. Are changes in the infrastructure needed? If so, why and what?

taught these medical students, there was not a formal mechanism for offsetting the expense through tuition revenue sharing. This is a more substantial problem in administrative structures in which the academic hospital is a separate legal entity from the university. Although there is generally a formal revenue sharing arrangement between the university and the hospital, there is seldom a similar arrangement between the university and the medical faculty.

Direct observations of programs being profiled here are consistent with findings of other studies that “teaching moments” increase the time spent for each clinical encounter by 20 to 30 percent. All programs examined for this study participated in fellowship training. Funding, with the exception

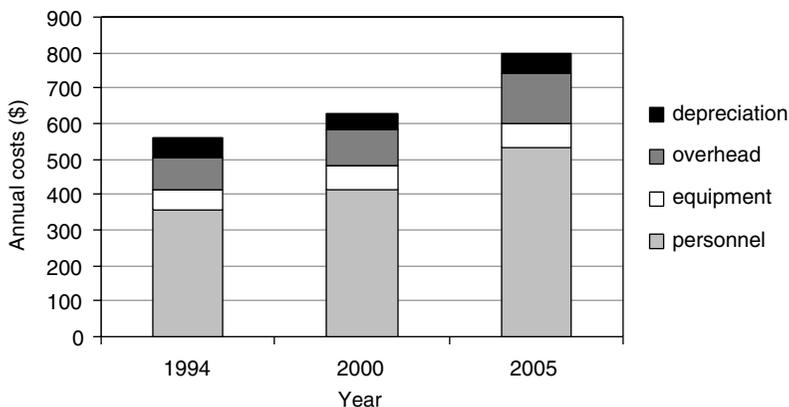


FIGURE 9-3 Direct service costs of sleep studies.

of direct NIH training grant support, was done without transparency and with minimal recognition of the expenses involved.

For research, there is a broad range of costs involved, depending on whether the research is basic or applied. This analysis focused only on direct costs and did not take into account start-up costs or shared or under-utilization of space or personnel costs.

Revenue Streams

There are three major clinical revenue streams: sleep studies—technical and professional components (the latter being for interpretation) and clinical encounters, teaching revenue streams (student tuition fees, graduate medical education [GME] funding, and NIH training grants), and one research revenue stream (grant funding both from federal and nonfederal sources).

Sleep studies generate the largest net revenue but mostly in the technical component. Clinical interpretations of sleep studies exhibited positive but lower margins. Clinical encounters were, at best, a breakeven proposition. This reflects general reimbursement patterns and the relatively higher overhead in academic practice by comparison to private practice settings. The relative efficiency of office practice varied considerably based on the organizational structure, but even under the best structure there was little evidence of net revenue beyond salary support for this part of the activity.

Interpretation of sleep studies does offer moderate net revenues even in the least efficient of the organizational structures. Direct costs are minimal, and federal and commercial insurance payments are predictable and above direct costs. Net revenue can support program development for both clinical

and teaching purposes. Whether a given sleep program can access the net revenue for development depends on the organizational structure and financial arrangements between the sleep program and its parent organization(s).

By far the greatest net revenue comes from sleep diagnostic procedures. However, compared with other outpatient procedures (e.g., endoscopy and surgery) and many inpatient procedures, the net revenue from sleep studies may represent a type of "opportunity cost," insofar as they are not as profitable as other procedures. The net revenue is sufficient, however, to support clinical, teaching, and research program development. Even so, whether a sleep laboratory is a potential source of programmatic reinvestment is very much affected by the entity that owns the laboratory. In a hospital setting, the sleep laboratory margins compete for space and personnel with other services that generate much higher net margins. The difficulty in acquiring sleep laboratory space and sharing in the revenue has resulted in many academic programs outsourcing sleep laboratory studies to private contractors. Revenue sharing plans, such as those at Emory University and the University of Pennsylvania, with private contractors can support clinical teaching.

Three sources of revenue for teaching include capture of student tuition, federal GME funding, and NIH training grants. However, none of the sleep programs profiled here received student tuition revenue despite the substantial time spent teaching students. This generally reflects funds flow in most academic centers and is therefore not specific to sleep programs. Training grants support the education of fellows during their research training. Support of the fellows' clinical education is derived from a variety of sources and therefore differs from one institution to another.

Federal and nonfederal research grants support the direct costs of research, but the indirect cost recovery, even when distributed, does not completely cover the overhead costs of doing research. Institutional supplements generally close the gap.

Findings About the Role of Organizational Structure

There are two major parameters defining the effect of organizational structure on academic sleep centers. The first is the relationships among the university, school of medicine, university hospital, and faculty practice group. The second is the relationship between the sleep program and the rest of the faculty practice groups.

Macrostructure

The relationships among the university, university hospital, and faculty group have a major bearing on transparency in career development, re-

source sharing, and program development. For a fortunate few, these organizational units exist within the same legal entity. For most, they are disaggregated, with many having the hospital as a separate legal entity. In others, the faculty practice group, hospital, and school of medicine are all separate legal entities. Under the disaggregated organizational structures, all the complications and barriers exist to multidisciplinary collaboration in clinical, teaching, and research activities. Even more relevant to the purpose of this report, the ability to reinvest net revenues generated by the various sleep programs' revenue streams is dependent on individual initiative, personal relationships, and historical fiscal arrangements.

Microstructure

The relationship between the sleep program and the rest of the faculty practice group controls program development. In a few instances, the program is a formally recognized administrative structure (either as a separate division or as a formal "center"). A formally recognized program enhances the likelihood of revenue and resource sharing, faculty recruitment and development, decisions about how to reinvest revenue, and the ability to respond to local conditions. All too often, however, the sleep program is informally recognized. Net revenues are folded back into the department—with no advantage to the sleep program. The sleep program often has little control over faculty selection and evaluation, risk of multiple sleep services being offered by competing departments, and significant barriers to cross-discipline teaching activities and credit. This, in turn, limits the program's capacity to attract new faculty of high quality. Consequently, most programs have relied on the charisma, determination, persistence, and persuasiveness of their program leader. However, successful sleep programs do not need to be established in separate administrative structures. Many large, successful programs with strong leadership are housed within long-established medical departments or divisions.

The degree of transparency (or lack thereof) in administrative policy and procedures governing cost and revenue allocation and the weighting of teaching and research activities relative to clinical income at both the individual faculty member and program level varied considerably. The integrated model demonstrated the greatest transparency, greatest growth, and least concern about how to reinvest in the program.

Summary of Fiscal and Organizational Analysis

Sleep programs can generate higher revenues than costs. The net revenues (i.e., profits) can be used for reinvestment to sustain and build the program. Programs studied here have three sources of revenues: grants,

clinical revenues, and teaching revenue. The technical revenue for sleep studies is the most profitable type of clinical revenue. It often is more profitable when contracted out to a private management firm with lower cost structures and more efficient operations. Contracting out also brings an added dividend: it gives the sleep program a dedicated source of revenue over which it may exert greater control. Training's financial benefits or disadvantages cannot be calculated, largely because none of the programs profiled here captured those costs.

The ability to control reinvestment in the sleep program is largely governed by the administrative structure within which the program is located. The ideal structure for controlling reinvestment exists when the program is a formal division within a medical school or the health science center—and when the medical school operates under the same administration as does the university hospital and faculty group. However, the committee recognizes that establishment of independent sleep departments is not possible in the vast majority of medical centers. Many successful sleep programs are divisions or centers in an existing medical department (e.g., internal medicine, neurology, or psychiatry). Therefore, facilitating growth of sleep programs can best occur by following the key principles previously set forth and the organization guidelines that will be discussed in the following section.

If the emphasis of the sleep program is on clinical services and clinical teaching, then the greatest reinvestment opportunities occur when the program is recognized as a formal clinical center, especially one that contracts out for sleep studies. If research is its greatest priority, then the greatest opportunities for program reinvestment occur when the sleep program is its own center administering its own grant activity.

Sleep programs have come into existence because of the vision and dedication of their leaders. Constructing a new enterprise requires that type of leadership, but sustaining and enhancing a program requires more: it requires a self-supporting organizational structure with transparent goals, rules of participation, and the capability to control reinvestment opportunities.

ACCREDITATION AND CERTIFICATION ARE ESSENTIAL TO QUALITY CARE

Although somnology and sleep medicine is a relatively new field, it is coming of age during this transformative period in medicine as a whole. Sleep medicine needs to be committed to the same high standards and evolving system of care influencing other fields of medicine, starting with the basics—accreditation and certification. The American Academy of Sleep Medicine (AASM) has standards for sleep centers, which include standards dealing with three broad functions: (1) accreditation of sleep centers and laboratories; (2) accreditation of sleep fellowship training programs;

and (3) certification of specialists in sleep medicine. Two of the AASM's functions recently have been assumed, at its request, by national certifying organizations (Table 9-1). The transition to these national certifying bodies is still in progress.

Accreditation of Sleep Centers or Laboratories

In 2005, the AASM accredited a total of 900 sleep centers and laboratories. There are two types of accreditation. One type, which accounts for the vast majority of accreditations (832 of 900), is a *sleep disorders center*. The centers are described as having a “comprehensive or full-service sleep disorders program” (American Academy of Sleep Medicine, 2006b). The other type of accreditation is for a more limited *laboratory for sleep-related breathing disorders only*.

The committee identified several problems with respect to quality of care. The foremost problem is that only 30 percent of sleep centers nationwide are accredited (Tachibana et al., 2005). Considering that an estimated 1 million polysomnograms were performed in 2001, it is likely that approximately 700,000 of them were not performed in accredited centers. Although there is no systematic evidence of poor quality of care in unaccredited centers, there is no assurance of quality care either. Because many of the serious health outcomes of sleep disorders may not manifest until years later, it would be difficult to link those outcomes with quality problems at the time of testing. Further, the fact that a majority of programs are not accredited taints the credibility of the field, preventing it from achieving the legitimacy that it has long sought.

TABLE 9-1 Evolution in Accrediting and Certifying Organizations in Somnology and Sleep Medicine

	Past Accrediting or Certifying Organization	Current Accrediting or Certifying Organization	Number Accredited or Certified in 2005
Sleep Centers or Laboratories	American Academy of Sleep Medicine	American Academy of Sleep Medicine	894 (832 centers, 62 labs)
Sleep Fellowship Training Programs	American Academy of Sleep Medicine	Accreditation Council for Graduate Medical Education	50 AASM 24 ACGME
Board Certification in Sleep Medicine	American Board of Sleep Medicine	American Board of Medical Specialties ^a	3,250

^aThe American Board of Medical Specialties will begin certification in 2007.

Finally, the absence of accreditation impedes sleep centers moving toward better care for patients (by embracing both diagnosis and treatment, rather than diagnosis alone). The overview to the standards indicates that accredited centers provide a comprehensive approach to patient care (AASM, 2006a). But this broad mission is not reflected in the actual criteria for accreditation. Accrediting criteria emphasize personnel, patient acceptance, facilities, and technical staff. The criteria lack specific emphasis on long-term disease management and improved outcomes provided by patient care. The committee heard testimony that many patients who are evaluated and diagnosed at centers are not systematically tracked in terms of follow-up care—either for treatment or for monitoring adherence with treatment. This testimony is consistent with research revealing that compliance with CPAP is poor (Kribbs et al., 1993; Reeves-Hoche et al., 1994). The committee could not find studies that directly address the extent to which diagnosed patients are not receiving treatment and follow-up care. The committee believes, however, that the accreditation procedure represents a unique opportunity to ensure that sleep centers are primarily focused on improving patient outcomes rather than diagnosis.

Accreditation of Fellowship Training Programs in Sleep Medicine

Starting in the mid-1990s, the AASM began to accredit sleep fellowship training programs. These are 1-year programs for medical doctors, which may be taken after completion of a residency (e.g., internal medicine, neurology, otolaryngology, psychiatry, or pediatrics or fellowships such as pulmonary medicine). In 2003, the ACGME approved AASM's application for transferring its fellowship training program to ACGME. AASM had actively sought approval in order to further elevate the standards for training and education. The newly established ACGME accreditation program began in June 2004. Accreditation criteria cover such areas as curriculum, qualifications of faculty, fellow competencies, scholarly activities, duty hours, and evaluation. By 2011, eligibility for board certification in sleep medicine will require attending an ACGME-accredited fellowship program in sleep medicine. Currently there are 24 ACGME-accredited fellowship programs and approximately 50 AASM accredited programs.

Certification of Specialists in Sleep Medicine

Since its inception, the AASM (or its predecessor organization) certified specialists by a specialty examination. By 1991, the AASM formed an independent body to serve that function, the American Board of Sleep Medicine. Certified professionals are known as diplomates in sleep medicine. The number of diplomates rose from 21 in the late 1970s to 3250 in 2005.

One of the board's major goals was realized in 2005, when it was accorded recognition as a bona fide subspecialty by the American Board of Medical Specialties. The timetable calls for a 6-year transition period. By 2011, board certification in sleep medicine will become available under the auspices of the American Boards of Internal Medicine, Pediatrics, Otolaryngology, and Psychiatry and Neurology. However, as discussed in Chapter 5, not all clinicians will be eligible to sit for the exam. The ACGME only permits accreditation of medical doctors; thus nurses, dentists, and doctorally prepared sleep specialists (e.g., psychologists and behavioral health specialists) in other fields will require alternative means of credentialing. It is possible that this may continue to be performed through the American Board of Sleep Medicine. Alternatively, other appropriate professional organizations may wish develop their own standards.

Health Insurance Role in Improving Quality

Health insurance, whether private or public (e.g., Medicare or Medicaid), is a driving force in health care delivery. Health insurance coverage drives the types of services that are offered and the incentives under which physicians operate. Health insurance coverage also influences who has access to services and how consumers select and use them (Hillman, 1991; Miller and Luft, 1994).

Health insurance coverage also influences the quality of care, often in unintentional ways. For example, fee-for-service health insurance may promote *overuse* of services—ones may not be necessary or that may expose patients to greater harm than benefit. Conversely, managed care may promote potential *underuse* of services from which patients might benefit (IOM, 2001). A major recommendation of the IOM report, *Crossing the Quality Chasm*, was to use health insurance as a means to ensure development of programs in quality improvement. Payment policies, the report recommended, should be used to reward higher quality of care.

The concept of using payment methods to reward better quality of care already has taken hold in many areas of medicine. It also is occurring in sleep medicine. In several regions, private health insurers require as a condition of reimbursement that sleep studies be conducted in accredited laboratories or centers (AASM, 2006a).

NEXT STEPS

Continued clinical advances and growth of the field depends on the appropriate emphasis and organization of academic sleep programs. These structures require special attention, not only to diagnosis, but also to long-term patient care that recognizes the need for chronic disease management

and strategies. The committee recommends a three-tier structure that ensures all academic health centers have at least a minimum set of organizational components that ensure adequate interdisciplinary clinical care, with subsequent tiers also emphasizing training and research components. Further, to ensure improved care and scientific advances, the committee recommends accreditation standards be updated to include patient care criteria.

Proposed Organizational Guidelines for Interdisciplinary Sleep Programs

As suggested throughout this chapter and the entire report, the current organizational structures at many academic health centers are not sufficient to ensure continued advances in clinical care and research. Consequently, the committee recommends that each health center strive to put in place an interdisciplinary sleep program. However, the committee recognizes that each of the 125 academic health centers has a different organizational structure and resources. Consequently, a three-tier model for interdisciplinary sleep programs is recommended, progressing from programs that emphasize clinical care and education, to programs with a considerable research capacity, advanced training, and public education (Table 9-2). The first tier

TABLE 9-2 Guidelines for Interdisciplinary Type I, II, and III Academic Sleep Programs

Attribute	Type I (clinical)	Type II (clinical, training, research)	Type III (regionalized comprehensive centers)
Structure and Composition			
Clinical specialties represented: ^a			
Internal medicine and relevant subspecialties	x	x	x
Neurology	x	x	x
Psychiatry and subdisciplines	x	x	x
Otolaryngology	x	x	x
Pediatrics and subspecialties (as necessary may be separate program)	x	x	x
Nursing	x	x	x
Psychology		x	x
Dentistry			x
Medical director certification in sleep medicine (American Board of Medical Specialties or American Board of Sleep Medicine) ^b	x	x	x
Consultant services from specialties not represented	x	x	x

TABLE 9-2 continued

Attribute	Type I (clinical)	Type II (clinical, training, research)	Type III (regionalized comprehensive centers)
Sleep specialists provide consultant services	x	x	x
Single accredited clinical sleep center	x	x	x
Comprehensive program for diagnosis and treatment of individuals	x	x	x
Training Program			
Training program for health care professionals and/or researchers	x	x	x
Medical school training and education	x	x	x
Education for residents in primary care	x	x	x
Residents in neurology, psychiatry, otolaryngology, and fellows in pulmonary medicine rotate through sleep program		x	x
Accredited fellowship program for physicians		x	x
Research training for clinical fellows		x	x
NIH-sponsored training grants for graduate and postgraduate researchers		x	x
Research Program			
Research areas of emphasis: ^c			
Neuroscience		x	x
Epidemiology/public health		x	x
Pharmacology			x
Basic <i>or</i> clinical research program		x	
Basic <i>and</i> clinical research program			x
Member of proposed national somnology and sleep medicine research and clinical network	x ^d	x	x
Regional coordinator for:			
Core facilities for basic research			x
Multisite clinical trials			x
Core facilities for clinical research			x
Mentoring of sleep fellows			x
Public education			x
Data coordinating site			x

^aThis list is not meant to be exclusive or exhaustive and should be modified as relevant specialties and training programs emerge.

^bCurrently this is American Board of Sleep Medicine. It is anticipated that in 2007 the examination would be supplanted by the American Board of Medical Specialties.

^cThis list is not meant to be exclusive or exhaustive. Other research areas could be involved (e.g., genetics, systems neurobiology, and bioengineering).

^dType I programs would be responsible for generating and submitting data to the national data registry established by the proposed national somnology and sleep medicine research and clinical network.

represents a comprehensive program that emphasizes diagnosis and patient care. Type II and III interdisciplinary programs require a progressively larger commitment to clinical care, research, and training.

It is the belief of the committee that, if these components and guiding principles are followed, interdisciplinary sleep programs can thrive, whether as a freestanding department or as a program within an existing department, division, or unit. There is the danger that establishing stand-alone centers will result in the formation of additional barriers. Therefore, academic sleep programs must be organized to limit the formation of silos and facilitate interdisciplinary care and research. In most academic health centers, faculty participating in a sleep program will likely continue to have their primary appointment in departments, programs, or centers. To ensure interdisciplinary research and care, as well as prevent the formation of additional silos, faculty appointed in sleep programs are encouraged to maintain a connection with both the sleep program and their primary appointment.

Many academic health centers have in place the components to establish these types of programs. However, organizing and coordinating the components to reach the committee's vision is not an inconsequential task. Not all academic health centers are currently positioned to create interdisciplinary sleep programs. The committee recognizes that there must be incentives to facilitate this transition. To achieve this lofty goal will take great effort by the leaders of sleep programs and support and commitment from academic leadership. Establishing Type II and Type III interdisciplinary programs will require additional support from the NIH. As discussed in Chapter 8, the increased availability of training grants and program project grants will also help aid the establishment of these programs. However, simply increasing the funding available for these activities may not be effective. It is important to also establish comprehensive interdisciplinary sleep programs that will provide an environment conducive for interdisciplinary sleep-related research, training, and career development. Finally, comprehensive patient care will also be facilitated through the creation of accreditation standards for interdisciplinary academic programs in Somnology and Sleep Medicine that cover the diagnosis, treatment, and long-term follow-up of individuals with sleep disorders. As discussed previously in this chapter, the AASM has a demonstrated track record and the expertise to develop these criteria, which could be expanded to include the overall management of sleep disorders.

The need to establish novel structures for Somnology and Sleep Medicine within academic health centers is in line with current changes occurring in many other areas of science and medicine. The organization of basic science departments in academic health centers has been in a continuing state of transition in recent years, according to new data analysis

from the American Association of Medical Colleges (AAMC). Medical schools are restructuring their basic science departments by consolidating the number of traditional departments and adding new departments to reflect scientific complexity and opportunity, as well as the changing nature of interdisciplinary biomedical research. The number of traditional discipline-based departments decreased from 2000 to 2004, but the overall number of departments has remained steady (Bunton 2006; Mallon et al., 2003). The creation of viable interdisciplinary sleep programs by the medical school leadership should benefit from ongoing experimentation in parallel areas.

Recommendation 9.1: New and existing sleep programs in academic health centers should meet the criteria of a Type I, II, or III interdisciplinary sleep program.

New and existing sleep programs should at a minimum conform to the criteria of a Type I clinical interdisciplinary sleep program. Academic medical centers with a commitment to interdisciplinary training are encouraged to train sleep scientists and fellows in sleep medicine, which would require at least a Type II training and research interdisciplinary sleep program. Research-intensive medical centers should aspire to become Type III regional interdisciplinary sleep programs and coordinators of the National Somnology and Sleep Medicine Research Network. The American Academy of Sleep Medicine should develop accreditation criteria for sleep programs specific to academic health centers.

Type I Clinical Interdisciplinary Sleep Program

The Type I Clinical Interdisciplinary Sleep Program, which if not already in existence, is achievable by the majority of centers nationwide and focuses on clinical care specialties. It further highlights the importance of increased awareness among health care professionals by requiring educational programs for medical students and residents in primary care. This minimum commitment to training is so important because of the sheer commonality of sleep disorders in primary care. Optimally, each academic health center should have a single Type I Clinical Interdisciplinary Sleep Program accredited center that emphasizes a comprehensive diagnosis and treatment program and includes representation from internal medicine and its relevant subspecialties, such as pulmonary medicine, neurology, psychiatry, otolaryngology, pediatrics, and nursing. Often pediatrics and its relevant subspecialties—especially in large, freestanding children’s hospitals—may be better served by a separate program. Further, this list of participating

specialties is not meant to be exclusive or exhaustive but should be modified as relevant specialties and training programs emerge. Although it is important that generalists and the key specialists are capable of treating individuals with sleep disorders, programs should also ensure that patients are referred to relevant specialists as needed. The medical director of each program should be certified in sleep medicine, and it should be a goal of each program that all physicians also be certified.

Type II Training and Research Interdisciplinary Sleep Program

A Type II Training and Research Interdisciplinary Sleep Program includes the characteristics of a Type I program but in addition is designed to provide optimal education, training, and research in somnology and sleep medicine. Nurses and psychologists should be included in the programs. Further, a Type II program should have an accredited fellowship program for all eligible physician rotations through the sleep program for all pulmonology, neurology, otolaryngology, and psychiatry residents. In addition, as described in Chapter 8, a Type II program would serve as an active member of the proposed National Somnology and Sleep Medicine Research and Clinical Network through at least an active basic or clinical research program. Research areas of emphasis should include, but not be limited to, science in the biological basis of sleep and population-based research on sleep patterns and problems.

Type III Regional Interdisciplinary Sleep Program

A Type III Regional Interdisciplinary Sleep Program includes the characteristics of Type I and II programs; however, in addition, a Type III program is designed to serve as a center for public health education, training for clinical care and research, basic research, patient-oriented research, translational research, and clinical care. As described in Chapter 8 the committee envisions that this type of program would act as a regional coordinator for the proposed National Somnology and Sleep Medicine Research and Clinical Network for education, training, mentoring, clinical care, research, clinical research studies, and large-scale population genetics studies. The committee does not recommend a specific number of Type III programs but recognizes that only a minimum number of programs currently have the necessary resources. However, as the field grows, more programs should develop the resources necessary to become a Type III program. Establishing these programs will not only require a significant investment from academic programs, but also, as described in Chapter 8, a long-term commitment by the NIH.

Chronic Care Accreditation Standards

As described earlier in this chapter, sleep disorders are chronic conditions with complex treatments. However, despite the importance of early recognition and treatment, the primary focus of most existing sleep centers is on diagnosis rather than on comprehensive management of sleep loss and sleep disorders as chronic conditions. This narrow focus may largely be the unintended result of compliance with criteria for accreditation of sleep laboratories, which emphasize diagnostic standards and reimbursement, for diagnostic testing. Clinical accreditation standards should be updated to address patient care needs.

Chronic disease management models, such as those used to provide optimal care for individuals with diabetes, asthma, congestive heart failure, and depression, have been proven to be effective at providing better-integrated care (Tsai et al., 2005). Therefore, the committee recommends that accreditation criteria for all sleep centers, embedded in either academic health centers or private sleep laboratories, be expanded to emphasize treatment, long-term patient care, and management strategies. Although sleep laboratories may face a financial burden implementing the changes, the committee believes this is the most effective way to ensure optimal patient care. Such criteria should be subject to further analysis and a demonstration that chronic care is a worthwhile investment. If such studies demonstrate a benefit, this may then change reimbursement patterns.

Recommendation 9.2: Sleep laboratories should be part of accredited sleep centers, the latter to include long-term strategies for patient care and chronic disease management.

All private and academic sleep laboratories should be under the auspices of accredited sleep centers and include adequate mechanisms to ensure long-term patient care and chronic disease management. Accreditation criteria should expand beyond a primary focus on diagnostic testing to emphasize treatment, long-term patient care, and chronic disease management strategies.

REFERENCES

- AASM (American Academy of Sleep Medicine). 2006a. *Standards for Accreditation of Sleep Disorders Centers*. [Online]. Available: <http://www.aasmnet.org/PDF/CenterStandards.pdf> [accessed January 3, 2006].
- AASM. 2006b. *Accreditation Standards*. [Online]. Available: <http://www.aasmnet.org/centerLab.aspx> [accessed January 18, 2006].
- Allison PJ, Nicolau B, Edgar L, Archer J, Black M, Hier M. 2004. Teaching head and neck cancer patients coping strategies: Results of a feasibility study. *Oral Oncology* 40(5):538–544.

- Baker TL, Guilleminault C, Nino-Murcia G, Dement WC. 1986. Comparative polysomnographic study of narcolepsy and idiopathic central nervous system hypersomnia. *Sleep* 9(1 pt 2):232–242.
- Benca RM. 2005. Diagnosis and treatment of chronic insomnia: A review. *Psychiatry Services* 56(3):332–343.
- Bodenheimer T, Wagner EH, Grumbach K. 2002. Improving primary care for patients with chronic illness. *Journal of the American Medical Association* 288(14):1775–1779.
- Bunton SA. 2006. Recent trends in basic science department reorganizations. *American Association of Medical Colleges Analysis in Brief* 6(1)1–21.
- Cherniack NS. 2005. Sleep apnea and insomnia: Sleep apnea plus or sleep apnea minus. *Respiration* 72(5):458–459.
- Chung KF. 2005. Insomnia subtypes and their relationships to daytime sleepiness in patients with obstructive sleep apnea. *Respiration* 72(5):460–465.
- Chung SA, Jairam S, Hussain MR, Shapiro CM. 2001. Knowledge of sleep apnea in a sample grouping of primary care physicians. *Sleep and Breathing* 5(3):115–121.
- Davidson JR, Waisberg JL, Brundage MD, MacLean AW. 2001. Nonpharmacologic group treatment of insomnia: A preliminary study with cancer survivors. *Psycho-Oncology* 10(5):389–397.
- Ehrenberg RG, Epifantseva J. 2001. Has the growth of science crowded out other things at universities? *Heldref Publications/Gale Group* 26:46–52.
- Ehrenberg RG, Rizzo MJ, Jakubson GH. 2003. *Who Bears the Growing Cost of Science at Universities?* [Online] Available: <http://www.nber.org/papers/w9627> [accessed December 15, 2005] (unpublished work).
- Epstein DR, Bootzin RR. 2002. Insomnia. *The Nursing Clinics of North America* 37(4):611–631.
- Hendricks JC, Finn SM, Panckeri KA, Chavkin J, Williams JA, Sehgal A, Pack AI. 2000. Rest in *Drosophila* is a sleep-like state. *Neuron* 25(1):129–138.
- Hillman AL. 1991. Managing the physician: Rules versus incentives. *Health Affairs (Millwood)* 10(4):138–146.
- IOM (Institute of Medicine). 2000. *To Err Is Human: Building a Safer Health System*. Washington, DC: National Academy Press.
- IOM. 2001. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: National Academy Press.
- Kapur V, Strohl KP, Redline S, Iber C, O'Connor G, Nieto J. 2002. Underdiagnosis of sleep apnea syndrome in U.S. communities. *Sleep and Breathing* 6(2):49–54.
- Kribbs NB, Pack AI, Kline LR, Smith PL, Schwartz AR, Schubert NM, Redline S, Henry JN, Getsy JE, Dinges DF. 1993. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *American Review of Respiratory Diseases* 147(4):887–895.
- Lach S, Schankerman M. 2001. Organizational structure as a determinant of academic patent and licensing behavior: An exploratory study of Duke, Johns Hopkins, and Pennsylvania State Universities. *Journal of Technology Transfer* 26(1):21–35.
- Lach S, Schankerman M. 2003. *Incentives and Invention in Universities*. [Online] Available: <http://www.nber.org/papers/w9727> [accessed December 15, 2005] (unpublished work).
- Lee K, Cho M, Miaskowski C, Dodd M. 2004a. Impaired sleep and rhythms in persons with cancer. *Sleep Medicine Reviews* 8(3):199–212.
- Lee KA, Landis C, Chasens ER, Dowling G, Merritt S, Parker KP, Redeker N, Richards KC, Rogers AE, Shaver JF, Umlauf MG, Weaver TE. 2004b. Sleep and chronobiology: Recommendations for nursing education. *Nursing Outlook* 52(3):126–133.
- Likar LL, Panciera TM, Erickson AD, Rounds S. 1997. Group education sessions and compliance with nasal CPAP therapy. *Chest* 111(5):1273–1277.

- Luski MB. 1958. *Interdisciplinary Team Research Methods and Problems*. Vol. 3. Research Training Series Edition. New York: New York University Press.
- Mallon WT, Biebuyck JF, Jones RF 2003. The reorganization of basic science departments in U.S. medical schools, 1980–1999. *Academic Medicine* 78(3):302–306.
- Miaskowski, C. 2004. Gender differences in pain, fatigue, and depression in patients with cancer. *Journal of the National Cancer Institute* (32):139–143.
- Miaskowski C, Lee KA. 1999. Pain, fatigue, and sleep disturbances in oncology outpatients receiving radiation therapy for bone metastasis: A pilot study. *Journal of Pain and Symptom Management* 17(5):320–332.
- Miller RH, Luft HS. 1994. Managed care plan performance since 1980. A literature analysis. *Journal of the American Medical Association* 271(19):1512–1519.
- Mock V, Pickett M, Ropka ME, Muscari Lin E, Stewart KJ, Rhodes VA, McDaniel R, Grimm PM, Krumm S, McCorkle R. 2001. Fatigue and quality of life outcomes of exercise during cancer treatment. *Cancer Practice* 9(3):119–127.
- National Academy of Sciences. 2004. *Facilitating Interdisciplinary Research*. Washington, DC: The National Academies Press.
- NHLBI (National Heart, Lung, and Blood Institute). 2003. *National Sleep Disorders Research Plan, 2003*. Bethesda, MD: National Institutes of Health.
- Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. 2000. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *Journal of the American Medical Association* 283(14):1829–1836.
- Parker KP, Kimble LP, Dunbar SB, Clark PC. 2005. Symptom interactions as mechanisms underlying symptom pairs and clusters. *Journal of Nursing Scholarship* 37(3): 209–215.
- Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE, Sleep Heart Health Study Investigators. 2004. Sleep-disordered breathing, glucose intolerance, and insulin resistance: The Sleep Heart Health Study. *American Journal of Epidemiology* 160(6):521–530.
- Rechtschaffen A, Bergmann BM, Everson CA, Kushida CA, Gilliland MA. 1989. Sleep deprivation in the rat: X. Integration and discussion of the findings. *Sleep* 12(1):68–87.
- Reeves-Hoche MK, Meck R, Zwillich CW. 1994. Nasal CPAP: An objective evaluation of patient compliance. *American Journal of Respiratory and Critical Care Medicine* 149(1): 149–154.
- Reuveni H, Tarasiuk A, Wainstock T, Ziv A, Elhayany A, Tal A. 2004. Awareness level of obstructive sleep apnea syndrome during routine unstructured interviews of a standardized patient by primary care physicians. *Sleep* 27(8):1518–1525.
- Richards K, Nagel C, Markie M, Elwell J, Barone C. 2003. Use of complementary and alternative therapies to promote sleep in critically ill patients. *Critical Care Nursing Clinics of North America* 15(3):329–340.
- Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Javier Nieto F, O'Connor GT, Boland LL, Schwartz JE, Samet JM. 2001. Sleep-disordered breathing and cardiovascular disease: Cross-sectional results of the Sleep Heart Health Study. *American Journal of Respiratory and Critical Care Medicine* 163(1):19–25.
- Shaw PJ, Cirelli C, Greenspan RJ, Tononi G. 2000. Correlates of sleep and waking in *Drosophila melanogaster*. *Science* 287(5459):1834–1837.
- Singh M, Drake C, Roehrs T, Koshorek G, Roth T. 2005. The prevalence of SOREMPs in the general population. *Sleep* 28(abstr suppl):A221.
- Spiegel K, Tasali E, Penev P, Van Cauter E. 2004. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Annals of Internal Medicine* 141(11):846–850.

- Sullivan CE, Issa FG, Berthon-Jones M, Eves L. 1981. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet* 1(8225):862–865.
- Tachibana N, Ayas TA, White DP. 2005. A quantitative assessment of sleep laboratory activity in the United States. *Journal of Clinical Sleep Medicine* 1(1):23–26.
- Taheri S, Lin L, Austin D, Young T, Mignot E. 2004. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Medicine* 1:210–217.
- Tsai AC, Morton SC, Mangione CM, Keeler EB. 2005. A meta-analysis of interventions to improve care for chronic illnesses. *American Journal of Managed Care* 11(8):478–488.
- Weaver TE, Laizner AM, Evans LK, Maislin G, Chugh DK, Lyon K, Smith PL, Schwartz AR, Redline S, Pack AI, Dinges DF. 1997. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep* 20(10):835–843.
- Young T, Evans L, Finn L, Palta M. 1997. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep* 20(9):705–706.

A

Study Process

The committee reviewed and considered a broad array of information in its work on issues involving sleep disorder research. Information sources included the primary scientific literature, books and scientific reviews, and presentations from researchers, as well as representatives from federal agencies and academic, professional, and nonprofit organizations.

LITERATURE REVIEW

Extensive bibliographic searches were conducted, resulting in a reference database of more than 2,000 entries. Searches of the primary biomedical bibliographic databases, MEDLINE and EMBASE,¹ were supplemented with searches of Dissertation Abstracts Online, LexisNexis, and THOMAS (a federal legislative database). The Dissertation Abstracts database provided information on the current level of Ph.D. thesis production in the field of sleep disorders.²

¹Excerpta Medica.

²Institute of Medicine staff searched the Dissertation Abstracts database using the search terms *sleep*, *sleep disorders*, *sleep apnea*, *dream*, *insomnia*, *hibernation*, *periodic limb movement*, *restless legs syndrome*, *circadian rhythm*, *narcolepsy*, and *sudden infant death syndrome*. The question mark is used to search for terms with multiple endings. For example, the search term *sleep disord?* resulted in hits that included *sleep disorder* and *sleep disorders*.

GRANT ANALYSIS

To identify information on funding mechanisms and trends from the National Institutes of Health (NIH), Institute of Medicine (IOM) staff queried the Computer Retrieval of Information on Scientific Projects (CRISP) database. This database collects information on the number of federally funded biomedical research projects. Data from the CRISP database were used to assess the number of fellowships (F grants), career grants (K grants), research grants (e.g., R01 grants), project grants (P grants), training (T grants), cooperative agreements (U grants), and Small Business Innovation Research and Small Business Technology Transfer awards funded by the NIH. To discern the number of NIH grants directed toward sleep-related research, IOM staff used appropriate keywords (which appeared in a 9,000-word thesaurus) for various sleep disorders, including: *insomnia*, *periodic limb movement disorder*, *restless legs syndrome*, *circadian rhythm*, *sudden infant death syndrome*, *sleep disorder*, *narcolepsy*, *sleep apnea*, *sleep*, *hibernation*, and *dream*. To limit the number of grants that were not relevant to somnology or sleep disorders the committee included only grants in which the keywords appeared in the thesaurus terms and not the abstract. Additional information on general funding trends at NIH was located in published documents and was provided by NIH staff.

PUBLIC WORKSHOPS

The committee held five meetings over the course of the study to address the study charge, review the data collected, and develop the report. Three of those meetings included public workshops: April 11–12, 2005; June 29–30, 2005; and September 15–16, 2005.

The first workshop (Box A-1) included three sessions that covered the public health significance of sleep deprivation and disorders, sleep deprivation and society, sleep apnea, and the impact of sleep deprivation and disorders on specific populations.

The committee held the second public workshop (Box A-2) in Washington, D.C. In that workshop the committee heard from 17 speakers who had expertise in surveillance and monitoring programs and technologies, model interdisciplinary programs, and training and education in sleep research.

The third meeting took place at the Jonsson Conference Center in Woods Hole, Massachusetts. The public workshop (Box A-3) consisted of two sessions that included a review of results from a survey and commissioned paper on sleep and a discussion with Dr. Charles Czeisler, director of Harvard Medical School's Division of Sleep Medicine and president-elect of the Sleep Research Society.

BOX A-1

**Institute of Medicine
Committee on Sleep Medicine and Research**

April 11–12, 2005

Monday April 11, 2005

Session I: Sponsors' Perspective, Panel Discussion with Committee

10:15 **National Sleep Foundation**
Richard Gelula, Executive Director

National Institutes of Health
Stuart Quan, Chair, NIH Sleep Disorders Research
Advisory Board
Carl Hunt, Director, National Center on Sleep Disorders
Research, National Heart, Lung, and Blood Institute
Merrill Mitler, Program Director, Extramural Research
Program, National Institute of Neurological Disorders
and Stroke

Sleep Research Society
Charles Czeisler, President-Elect
Jerry Barrett, Executive Director

American Academy of Sleep Medicine
Michael Sateia, President
Lawrence Epstein, President-Elect
Jerry Barrett, Executive Director
Jennifer Markkanen, Assistant Executive Director

Tuesday, April 12, 2005

Session I: Public Health Significance of Sleep Deprivation and Disorders

8:25 **Welcome and Introductions**
Harvey Colten, Chair

8:30 **Impact of Insomnia and Periodic Leg Movements**
Thomas Roth, Henry Ford Health System of Detroit

9:00 **Overview of the Public Health Significance of Sleep
Deprivation and Disorders**
Terry Young, University of Wisconsin

continued

BOX A-1 continued

9:30 **Sleep Duration: Neurobehavioral, Physiological, and Epidemiological Issues**

David Dinges, University of Pennsylvania School of Medicine

Session II: Sleep Deprivation and Society

10:15 **Accidents Caused by Sleep Deprivation and Disorders**

Allan Pack, University of Pennsylvania Medical Center

10:45 **Metabolic Consequences of Sleep Deprivation**

Daniel Gottlieb, Boston University School of Medicine

Session III: Sleep Apnea

11:15 **Effect of Apnea on Cardiovascular Disease and Metabolic Functions**

Susan Redline, Case Western Reserve University School of Medicine

11:45 Discussion of Morning Session

Session IV: Impact of Sleep Deprivation and Disorders on Specific Populations

1:00 **Snoring in Children: Sound the Alarm!**

David Gozal, University of Louisville

1:30 **Sleep Loss and Women's Health**

Kathy Lee, University of California, San Francisco

2:00 **Sleep Disturbance in Geriatrics**

Donald Bliwise, Emory University

2:30 Discussion of Afternoon Session

BOX A-2

**Institute of Medicine
Committee on Sleep Medicine and Research**

June 29–30, 2005

June 29, 2005

11:15 **Lee Goldman**
 University of California, San Francisco, Department of
 Medicine

Surveillance Programs and Technologies

1:00 **Welcome and Introductions**
 Harvey Colten, Chair
 Paul Eggers, NIDDK, Co-Project Officer, United States
 Renal Data System
 Ed Sondik, Director, National Center for Health Statistics

2:15 **Open Discussion**

2:45 **Roger Rosa**
 Senior Scientist, National Institute for Occupational Safety
 and Health

3:15 **Eugene J. Lengerich**
 Co-Chair, Pennsylvania Cancer Control Consortium

3:45 **Andrea Califano**
 Co-Director, Center for Computational Biochemistry and
 Biosystems, Bioworks and the NCI caCORE platform

4:15 Open Discussion

June 30, 2005

Organizational Impediments

8:30 **David Lewis**
 President and Chief Executive Officer, SleepMed, Inc.

9:00 **Michael Martin**
 Director of the Division of Physiology and Pathology in the
 Center for Scientific Review, NIH

continued

BOX A-2 continued

- 9:30 **William Dement**
 Director, Sleep Research Center, Stanford University
 School of Medicine
- 10:15 **David White**
 Director, Sleep Disorders Program, Brigham and Women's
 Hospital
- 10:45 General Discussion

Model Interdisciplinary Programs

- 12:30 **Kathleen C. Buckwalter**
 Codirector University of Iowa Center on Aging
- 1:00 **Story Landis**
 Director, NINDS, Co-chair NIH Pain Consortium
- 1:30 **Hal Moses**
 Founding Director of the Vanderbilt-Ingram Cancer
 Center
- 2:00 **David J. Kupfer**
 Chair, Department of Psychiatry, University of Pittsburgh
 School of Medicine
- 2:30 **Steven Wolinsky**
 Division Chief of Infectious Diseases
 Northwestern University
- 3:00 General Discussion

Training and Education

- 3:30 **Judith Owens**
 Brown University Medical School, AASM MED Sleep
 Program
- 4:00 **Daniel Buysse**
 Department of Psychiatry, UPMC Sleep Medicine Center
 and Sleep Medicine Fellowship Training Program
- 4:30 **Roger Bulger**
 President, Association of Academic Health Centers
- 5:00 General Discussion

BOX A-3

**Institute of Medicine
Committee on Sleep Medicine and Research**

September 15–16, 2005

September 15, 2005

12:45 **Results from AASM Academic Health Centers Survey**
Michael Sateia, Section of Sleep Medicine Chief,
Dartmouth University
Past President, American Academy of Sleep Medicine

1:30 **Preliminary Findings of Commissioned Paper**
John Fontanesi, Center for Management Science in
Public Health, University of California, San Diego

September 16, 2005

10:15 **Discussion with Charles Czeisler**
Director, Division of Sleep Medicine, Harvard Medical School
President-Elect, Sleep Research Society

B

Acronyms

AASM	American Academy of Sleep Medicine
ABSM	American Board of Sleep Medicine
ACGME	Accreditation Council for Graduate Medical Education
ADHD	attention-deficit hyperactivity disorder
ADSM	Academy of Dental Sleep Medicine
AHI	apnea-hypopnea index
AMA	American Medical Association
APSS	annual meeting of sleep professional societies
ASAA	American Sleep Apnea Association
ATS	American Thoracic Society
BEARS	B = bedtime issues, E = excessive daytime sleepiness, A = night awakenings, R = regularity and duration of sleep, S = snoring
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CNS	central nervous system
CPAP	continuous positive airway pressure
CRISP	Computer Retrieval of Information on Scientific Projects
CRP	C-reactive protein
CSA	central sleep apnea
CSF	cerebrospinal fluid

DCI	Diseases and Conditions Index
DNA	deoxyribonucleic acid
EEG	electroencephalogram
GABA	gamma-aminobutyric acid
HCRT	hypocretin
HLA	human leukocyte antigen
HPA	hypothalamic-pituitary axis
IRG	integrated review groups
L-DOPA	levo-dopa
MEPS	Medical Expenditure Panel Survey
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MS	multiple sclerosis
MSLT	multiple sleep latency test
NAMCS	National Ambulatory Medical Care Survey
NCHS	National Center for Health Statistics
NCMRR	National Center for Medical Rehabilitation Research
NCSDR	National Center for Sleep Disorders Research
NEHS	National Employer Health Insurance Survey
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHDS	National Hospital Discharge Survey
NHHCS	National Home and Hospice Care Survey
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NHPI	National Health Provider Inventory
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NNHS	National Nursing Home Survey
NREM	nonrapid eye movement
NSAS	National Survey of Ambulatory Surgery
NSF	National Sleep Foundation
NTSB	National Transportation Safety Board

OSA	obstructive sleep apnea
PA	program announcement
PLMI	periodic limb movement index
PSG	polysomnography
REM	rapid eye movement
RFA	request for application
RLS	restless legs syndrome
RNA	ribonucleic acid
SAA	sleep academic award
SBIR	Small Business Innovative Research
SCN	suprachiasmatic nucleus
SCOR	specialized center of research
SDB	sleep-disordered breathing
SIDS	sudden infant death syndrome
SOREMP	sleep onset REM period
SRS	Sleep Research Society
SWS	slow-wave sleep
WASO	wake time after sleep onset
YRBSS	Youth Risk Behavior Surveillance System

C

Glossary of Major Terms

- Acoustic reflectometry** A technique that allows for noninvasive measurement of human airways to quantify anatomical obstruction of the upper airway.
- Actigraph** A movement detector coupled with software that uses movement patterns to diagnose sleep disorders.
- Adenoid** An enlarged mass of lymphoid tissue at the back of the nasopharynx that, when enlarged, can obstruct the nasal and ear passages, forcing respiration through the mouth and inducing nasality, postnasal discharge, and dullness of facial expression.
- Adenotonsillectomy** The surgical removal of tonsils and adenoids.
- African trypanosomiasis** A category of disease caused by infection with the *Trypanosoma brucei* (*Tb*) parasite and resulting in sleeping sickness.
- Antihypertensive** A class of drugs that are used to reduce high blood pressure.
- Antipsychotic** A powerful tranquilizer typically used to treat psychosis.
- Apnea** Transient stop of respiration due to either normal or abnormal causes.
- Apnea-hypopnea index** The total number of episodes of apnea and hypopnea per hour of sleep. A value of 5 or greater is abnormal and may be associated with excessive daytime sleepiness.
- Atonia** Lack of physiological muscle tone.
- Attention-deficit/hyperactivity disorder (ADHD)** A syndrome of disordered learning and disruptive behavior, with no known cause, and characterized by one or all of the following symptoms: inattentiveness,

hyperactivity, and impulsive behavior. Also known as attention deficit disorder (ADD).

Autoimmune Referring to or caused by autoantibodies or white blood cells that attack molecules, cells, or tissues of the organism producing them.

BEARS A 5-step pediatric sleep screening form to identify sleep problems (B = bedtime issues, E = excessive daytime sleepiness, A = night awakenings, R = regularity and duration of sleep, S = snoring).

Body mass index (BMI) A measure of body fat that is the ratio of the weight of the body in kilograms to the square of its height in meters.

Carotid body A small body of vascular tissue that is able to sense changes in the partial pressures of oxygen and carbon dioxide in the blood and to mediate reflex changes in respiration.

Cataplexy A symptom of narcolepsy, characterized by a sudden loss of muscle control with retention of clear consciousness in response to a strong emotional stimulus.

Catecholamine An amine (such as norepinephrine or dopamine), derived from tyrosine, that functions as a neurotransmitter, hormone, or both.

Central sleep apnea Cessation of breathing during sleep that is caused a disturbance in the brain's respiratory center.

Cerebral cortex The surface layer of the brain's gray matter, which coordinates sensory and motor information.

Cerebrospinal fluid (CSF) A liquid that is secreted from the blood into the internal cavities in each cerebral hemisphere of the brain and circulates through the cavities to the spaces formed between the brain or spinal cord and the surrounding membranes; serves chiefly to maintain uniform pressure within the brain and spinal cord.

Chemoreflex A physiological reflex initiated in a chemoreceptor or in response to a chemical stimulus.

CHQ-PF50 A parent report measure of children's physical, emotional, and social functional status and well-being.

Chronobiology The science of biological rhythms.

Circadian rhythms 24-hour periods or cycles of biological activity or function.

Cognitive therapy Psychotherapeutic method aimed at changing faulty beliefs and attitudes about sleep, insomnia, and the next-day consequences. Other cognitive strategies are used to control intrusive thoughts at bedtime and prevent excessive monitoring of the daytime consequences of insomnia.

Confusional arousal One type of disorder of arousal associated with NREM sleep. Individuals display mental confusion or confusional behavior during or following arousal, typically from slow-wave sleep.

- Corticosteroids** Any of various adrenal-cortex steroids used medically, especially as anti-inflammatory agents.
- Dementia** A condition characterized by the progressive development of multiple cognitive deficits, such as memory impairment, difficulty in speech comprehension and production, and inability to plan and initiate complex behavior.
- Dialysis** A category of medical procedures to remove wastes or toxins from the blood and adjust fluid and electrolyte imbalances.
- Diurnal** Occurring in the daytime.
- Dysesthesia** The impairment of tactile sensitivity.
- Electroencephalograph (EEG)** Machine used to monitor and categorize sleep stages by measuring changes in brain wave activity.
- Electro-oculogram** A record of the standing voltage between the front and back of the eye that is correlated with eyeball movement (as in REM sleep) and obtained by electrodes suitably placed on the skin near the eye.
- Electrophysiology** The study of the electrical activity related to physiological function of living tissue.
- Epilepsy** A category of disorders characterized by abnormal electrical activity in the brain and featuring symptoms such as sudden brief episodes of altered or diminished consciousness, involuntary movements, or convulsions.
- Epworth sleepiness scale** A series of questions used to determine whether an individual is sleepy or not.
- Excessive daytime sleepiness** Background of constant sleepiness with sleep attacks leading to unintended napping during the day; a characteristic symptom of narcolepsy.
- Exploding head syndrome** Characterized by a sudden, loud noise or explosion in the head, this is an imagined, painless noise.
- F30 fellowship** Individual Predoctoral National Research Service Award for M.D./Ph.D. degrees. Fellowship award that provides combined medical school and predoctoral Ph.D. support for a maximum of 6 years.
- F31 fellowship** Predoctoral Individual National Research Service Award. Fellowship award that provides up to 5 years of support for research training leading to the Ph.D. or equivalent research.
- F32 fellowship** Postdoctoral Individual National Research Service Award. Fellowship award that provides postdoctoral research training to broaden scientific background.

F33 fellowship National Research Service Award for Senior Fellow. Fellowship award that provides opportunities for experienced scientists to broaden scientific background.

Gene A DNA sequence that encodes a protein.

Gene loci The term used to describe the locations of genes on a chromosome.

Generalized anxiety disorder An anxiety disorder characterized by chronic excessive anxiety and worry that is difficult to control, and it consequently impairs daily functioning and causes stress. Primary symptoms include: restlessness, irritability, poor concentration, and sleep disturbances.

Hemodialysis The removal and purification of blood from an artery, followed by the addition of vital substances and reintroduction into the circulatory system through a vein.

Hypersomnia Periods of normal duration of sleep and waking are interspersed with excessive periods of sleep.

Hypersomnolence Excessive drowsiness.

Hypertension Abnormally high arterial blood pressure that typically results in a thickening and inelasticity of arterial walls and left heart ventricle hypertrophy. A risk factor for various pathological conditions or events such as heart attack, heart failure, stroke, end-stage renal disease, or retinal hemorrhage.

Hypnagogic Relating to or occurring in the drowsiness stage that immediately precedes the onset of sleep.

Hypnagogic hallucinations A characteristic symptom of narcolepsy that is marked by frightening dreamlike REM sleep experiences when falling asleep.

Hypnopompic Referring to the semiconsciousness period that precedes waking.

Hypnopompic hallucinations A characteristic symptom of narcolepsy that is marked by frightening dreamlike REM sleep experiences when waking up from sleep.

Hypnotic An agent that induces sleep.

Hypocretin-1 One of a pair of highly excitatory neuropeptide hormones (the other being hypocretin-2) that are biosynthesized in the hypothalamus and are involved in the cause of narcolepsy-cataplexy. Also known as orexin-A.

Hypopnea Extremely shallow or abnormally slow respiration.

Hypoxia Impaired oxygenation of the tissues of the body.

- Insomnia** A prolonged and usually abnormal inability to obtain adequate sleep that may result in sleepiness, fatigue, difficulty concentrating, and irritability.
- Interleukin** Compounds of low molecular weight that chiefly function in immune system regulation and cell-mediated immunity.
- K award** Career development awards offered by the NIH to assist new investigators at stages beyond postdoctoral training in order to become independent scientists. Support for the awards is limited to one 3- to 5-year term and is usually restricted to one mentored career award per individual.
- K01 award** Mentored Research Scientist Development Award. Provides salary and fringe benefits for awardees for career development experience.
- K02 award** Independent Scientist Award. Provides up to 5 years of salary and fringe benefit support for newly independent scientists.
- K05 award** Senior Scientist Award. Provides salary and fringe benefit support for outstanding scientists to enhance skills in their research field.
- K07 award** Academic Career Award. Provides up to 5 years of funding to develop or improve curricula changes that emphasize development and leadership skills of scientists.
- K08 award** Mentored Clinical Scientist Development Award. Provides salary and fringe benefit support for the development of clinician research scientists.
- K12 award** Mentored Clinical Scientist Development Program Award. Provides support to an educational institution for career development experiences for clinicians leading to research independence.
- K23 award** Mentored Patient-Oriented Research Career Development Award. Provides salary and fringe benefit support for the development of patient-oriented research scientists.
- K24 award** Midcareer Investigator Award in Patient-Oriented Research. Provides salary and fringe benefit support to allow protected time for patient-oriented research and time to act as mentors for beginning clinical investigators.
- K25 award** Mentored Quantitative Research Career Development Award. Provides salary and fringe benefit support for career development for scientists with quantitative and engineering backgrounds to foster interdisciplinary collaboration in biomedical research.
- K-complex** Negative sharp waves followed immediately by slower positive component; sleep spindles may ride on K-complexes. May occur in response to sound or spontaneously but may be distinguished from background activity on the EEG.

Kleine-Levin syndrome Characterized by recurrent episodes of dramatic hypersomnia lasting from 2 days to several weeks. These episodes are associated with behavioral and cognitive abnormalities, binge eating or hypersexuality, and alternate with long asymptomatic periods that last months to years.

Leptin A peptide hormone produced by fat cells and involved in the regulation of body weight by acting on the hypothalamus to suppress appetite and burn fat stored in connective tissue.

Magnetic resonance imaging (MRI) A type of diagnostic imaging technique that relies on the interactions of magnetic fields and radio-frequency radiation with body tissues.

Melatonin A vertebrate hormone that has been linked to circadian rhythm regulation, is derived from serotonin, and is secreted by the pineal gland especially in response to darkness.

Multiple Sleep Latency Test (MSLT) A test that objectively quantifies daytime sleepiness.

Myoclonic epilepsy Epilepsy characterized by myoclonic seizures, which involve brief and involuntary contractions of a muscle.

Narcolepsy A chronic neurological condition marked by transient attacks of deep sleep, with symptoms of cataplexy, hypnagogic hallucinations, sleep disruption, and sleep paralysis.

Nares The pair of openings of the nose.

Nightmare disorder Recurrent nightmares that are coherent dream sequences and manifest as disturbing mental experiences, generally occurring during REM sleep.

Night terrors One type of disorder of arousal associated with NREM sleep. Typically initiated by a loud scream associated with panic, followed by intense motor activity, which can result in injury.

Nocturnal groaning Characterized by disruptive groaning that occurs during expiration, particularly during the second half of night. Also known as catathrenia.

Non-rapid eye movement sleep (NREM) A state of deep, usually dreamless, sleep that occurs regularly during a normal period of sleep with intervening periods of REM sleep and is characterized by delta waves and a low level of autonomic physiological activity—called also non-REM sleep or slow-wave sleep.

Obstructive sleep apnea (OSA) Obstructive sleep apnea is caused by recurrent interruption of breathing during sleep due to upper airway obstruction caused by sleep-related loss of upper airway muscle tone or anatomical obstruction of the upper airway. Also called obstructive sleep apnea syndrome.

P01 grant Federally supported research program project grant that is sponsored by the National Institutes of Health and that funds as many as

three separate, multidisciplinary research projects that are based on a central research theme. Funding is limited to about \$1 million each year in direct costs.

P20 grant Federally supported research program project grant that is sponsored by the National Institutes of Health and that funds exploratory grants. Provides support for the development of new or interdisciplinary programs or the expansion of existing resources.

P30 grant Federally supported center core grant that is sponsored by the National Institutes of Health and that provides funds to develop an infrastructure that supports centralized research, facilities, and resources. Core grants provide resources to investigators to help them achieve a higher level of productivity. Awards are limited to 5 years and about \$500,000 in direct costs per year.

P50 grant Federally supported specialized center grant that is sponsored by the National Institutes of Health and that provides funds for multi-investigator, multidisciplinary research. Funding is limited to about \$1 million each year in direct costs.

Parasomnia Unpleasant or undesirable behaviors or experiences that occur during entry into sleep, during sleep, or during arousals from sleep.

Pharyngeal Relating to or located in the pharynx area.

Polysomnogram A sleep test that continuously acquires physiological data obtained during sleep, including brain wave activity, eye movements, muscle activity (chin and legs), heart rate, body position, and respiratory variables, including oxygen saturation.

Polysomnography Use of a polygraph to record multiple physiological variables during sleep.

Prader-Willi syndrome A genetic disorder marked by mental retardation, below average height, hypotonia, abnormally small hands and feet, gonadal incompetence, and excessive appetite resulting in extreme obesity.

R01 award Federal research project grant that supports specific health-based research for 1 to 5 years. It can be investigator initiated or submitted in response to a request for application or program announcement.

R03 award Federal grant that supports small research projects for a limited period of time and with limited resources. Grants are awarded for up to 2 years with direct costs limited to \$50,000 per year.

R13 award Federal grant that supports conference grants. Provides support for a symposium, seminar, workshop, or other formal conference assembled to exchange and disseminate information or to explore a subject, problem, or field of knowledge.

- R21 award** Federally supported exploratory or developmental research grant that supports the early development of an innovative project. Grants are awarded for up to 2 years, with total direct costs not to exceed \$275,000 for the length of the project.
- R25 award** Federal grant that supports education project grants. Provides support to develop a program in education, information, training, technical assistance, or evaluation.
- Rapid eye movement (REM)** Rapid and simultaneous movement of both eyes, and associated with REM sleep.
- Rapid eye movement sleep** A state of sleep that is experienced in several cycles during a normal period of sleep and is marked by increased forebrain and midbrain neuronal activity and by reduced muscle tone. Humans experience dreams, rapid eye movements, and vascular congestion of the sex organs during REM sleep.
- Rapid eye movement sleep behavior disorder** A complex set of behaviors, including mild to harmful body movements associated with dreams and nightmares and loss of muscle atonia.
- Restless legs syndrome (RLS)** A neurological condition characterized by an irresistible urge to move that occurs or worsens at rest and is relieved by activity. It is also sometimes characterized by worsening in the evening and night.
- Sleep apnea** A condition marked by transient cessation of breathing during sleep, as a result of either airway obstruction or a disturbance in the brain's respiratory center. Especially associated with excessive daytime sleepiness.
- Sleep drunkenness** Difficulty waking up and being foggy for long periods of time after wake onset. Also known as sleep inertia.
- Sleep hygiene** Describes the practice of maintaining proper sleep health.
- Sleep medicine** A branch of clinical medicine devoted to the diagnosis and treatment of individuals suffering from chronic sleep loss or sleep disorders.
- Sleep paralysis** Muscle paralysis akin to REM sleep atonia while awake, when falling asleep, or waking up.
- Sleep-related dissociative disorder** A dissociative episode that can occur in the period from wakefulness to sleep or from awakening from stages 1 or 2 or from REM sleep.
- Sleep-related eating disorder** Marked by repeated episodes of involuntary eating and drinking during arousals from sleep.
- Sleep-related hallucination** Hallucinatory images that occur at sleep onset or on awakening from sleep.
- Sleep restriction therapy** A method to curtail time in bed to the actual sleep time, thereby creating mild sleep deprivation, which results in more consolidated and more efficient sleep.

- Sleep spindle** Waxing and waning electrical brain activity at 7 to 14 Hz, grouped in sequences that last 1 to 2 seconds and recur periodically with a slow rhythm of 0.1 to 0.4 Hz. Typically appear during sleep stage 2.
- Sleepwalking** One type of disorder of arousal associated with NREM sleep. Involves a series of behaviors initiated during arousals from slow-wave sleep that culminate in walking around in an altered state of consciousness.
- Slow-wave sleep (SWS)** Term used to describe sleep stages 3 and 4 together due to characteristic slow waves.
- Somnology** The branch of science devoted to the study of the physiology of sleep, the behavioral dimensions of sleep, and the consequences of sleep loss and sleep disorders on an individual's and the general population's health, performance, safety, and quality of life.
- Somnolence** Drowsiness.
- Spasticity** A state of increased muscular tone in which abnormal stretch reflexes intensify muscle resistance to passive movements.
- Stage 1 sleep** First stage of NREM sleep characterized by low-voltage, mixed frequency waves on the EEG; small eye movements; and tonic muscles.
- Stage 2 sleep** Second stage of NREM sleep characterized by low-voltage, mixed frequency waves on the EEG, sleep spindles, and K-complexes; occasional small eye movements near sleep onset; and tonic muscles.
- Stage 3 sleep** Third stage of NREM sleep characterized by high-voltage, slow-wave activity on EEG; no eye movements; and tonic muscles.
- Stage 4 sleep** Fourth stage of NREM sleep characterized by high-voltage, slow-wave activity on EEG; no eye movements; and tonic muscles.
- Sudden Infant Death Syndrome (SIDS)** The death of an apparently healthy infant usually before 1 year of age that is of unknown cause and occurs especially during sleep.
- Suprachiasmatic nucleus (SCN)** Either of a pair of neuron clusters in the hypothalamus that receive visual information from the retina via the optic nerve and that regulate the body's circadian rhythms.
- T32 training grant** National Research Service Award Institutional Research Training Grants. Provides support to institutions to develop or enhance research training opportunities for predoctoral and post-doctoral students.
- T34 training grant** National Research Service Award Institutional Undergraduate Research Training Grant. Provides support to institutions to promote undergraduate research training to underrepresented groups in the biomedical and behavioral sciences.

T35 training grant Short-Term Institutional Research Training Grant. Provides support to institutions for predoctoral and postdoctoral training focused on biomedical and behavioral research.

Type 2 diabetes mellitus Diabetes that develops especially in adults and especially in obese individuals. Marked by high blood sugar that is a consequence of impaired insulin utilization and a physiological inability to compensate with increased insulin production. Also called adult-onset diabetes, late-onset diabetes.

U Cooperative Agreements Provided to support any part of the full range of research and development activities composing a multidisciplinary attack on a specific disease entity or biomedical problem area.

D

Congressional Language Establishing the National Center on Sleep Disorders Research, § 285b–7

The following is the congressional language that was part of the 1993 National Institutes of Health (NIH) Revitalization Act, which created the National Center on Sleep Disorders Research. The NIH Revitalization Act became law (*P.L. 103-43*) on June 10, 1993.

- a) **Establishment** Not later than 1 year after June 10, 1993, the Director of the Institute shall establish the National Center on Sleep Disorders Research (in this section referred to as the “Center”). The Center shall be headed by a director, who shall be appointed by the Director of the Institute.
- b) **Purpose** The general purpose of the Center is—
 - 1. the conduct and support of research, training, health information dissemination, and other activities with respect to sleep disorders, including biological and circadian rhythm research, basic understanding of sleep, chronobiological and other sleep related research; and
 - 2. to coordinate the activities of the Center with similar activities of other Federal agencies, including the other agencies of the National Institutes of Health, and similar activities of other public entities and nonprofit entities.
- c) **Sleep Disorders Research Advisory Board**
 - 1. The Director of the National Institutes of Health shall establish a board to be known as the Sleep Disorders Research Advisory Board (in this section referred to as the “Advisory Board”).

2. The Advisory Board shall advise, assist, consult with, and make recommendations to the Director of the National Institutes of Health, through the Director of the Institute, and the Director of the Center concerning matters relating to the scientific activities carried out by and through the Center and the policies respecting such activities, including recommendations with respect to the plan required in subsection (c)¹ of this section.
3.
 - A. The Director of the National Institutes of Health shall appoint to the Advisory Board 12 appropriately qualified representatives of the public who are not officers or employees of the Federal Government. Of such members, eight shall be representatives of health and scientific disciplines with respect to sleep disorders and four shall be individuals representing the interests of individuals with or undergoing treatment for sleep disorders.
 - B. The following officials shall serve as ex officio members of the Advisory Board:
 - i. The Director of the National Institutes of Health.
 - ii. The Director of the Center.
 - iii. The Director of the National Heart, Lung, and Blood Institute.
 - iv. The Director of the National Institute of Mental Health.
 - v. The Director of the National Institute on Aging.
 - vi. The Director of the National Institute of Child Health and Human Development.
 - vii. The Director of the National Institute of Neurological Disorders and Stroke.
 - viii. The Assistant Secretary for Health.
 - ix. The Assistant Secretary of Defense (Health Affairs).
 - x. The Chief Medical Director of the Veterans' Administration.
4. The members of the Advisory Board shall, from among the members of the Advisory Board, designate an individual to serve as the chair of the Advisory Board.
5. Except as inconsistent with, or inapplicable to, this section, the provisions of section 284a of this title shall apply to the advisory board established under this section in the same manner as such provisions apply to any advisory council established under such section.

¹So in original. Probably should be subsection "(d)".

d) **Development of comprehensive research plan; revision**

1. After consultation with the Director of the Center and the advisory board established under subsection (c) of this section, the Director of the National Institutes of Health shall develop a comprehensive plan for the conduct and support of sleep disorders research.
2. The plan developed under paragraph (1) shall identify priorities with respect to such research and shall provide for the coordination of such research conducted or supported by the agencies of the National Institutes of Health.
3. The Director of the National Institutes of Health (after consultation with the Director of the Center and the advisory board² established under subsection (c) of this section) shall revise the plan developed under paragraph (1) as appropriate.

e) **Collection and dissemination of information** The Director of the Center, in cooperation with the Centers for Disease Control and Prevention, is authorized to coordinate activities with the Department of Transportation, the Department of Defense, the Department of Education, the Department of Labor, and the Department of Commerce to collect data, conduct studies, and disseminate public information concerning the impact of sleep disorders and sleep deprivation.

²So in original. Probably should be capitalized.

E

Sleep Disorders Research Advisory Board Membership

Name	Affiliation	Year of Term Expiration
Scientific and Health		
Wayne E. Crill, MD	Professor and chair, Department of Physiology and Biophysics, School of Medicine, University of Washington	1996
Debra J. Meyers, MD	Private Physician Pulmonary Associates	1996
Thomas Roth, PhD	Director, Sleep Disorders and Research Center, Henry Ford Hospital	1996
J. Christian Gillin, MD	Professor, Department of Psychiatry/UCSD/VAMC	1997
Allan Pack, MB, ChB, PhD	Director of Medicine Center on Sleep and Respiratory Neurobiology, Hospital of the University of Pennsylvania	1997
Barbara A. Phillips, MD, MSPH	Professor, Division of Pulmonary and Critical Care; Medicine Director, Sleep Apnea Laboratory, University of Kentucky and Good Samaritan Hospitals	1997
James K. Walsh, PhD	Director, Sleep Medical Center St. Luke's MSPH	1997
Sudhansu Chokroverty, MD	Professor and associate chair of neurology; chief of neurophysiology, Department of Neurology, St. Vincent's Hospital & Medical Center	1998
Martha U. Gillette, PhD	Professor, Department of Cell and Structure Biology, University of Illinois	1999

Name	Affiliation	Year of Term Expiration
Fred W. Turek, PhD	Director, Center for Circadian Biology & Medicine; professor and chair, Department of Neurobiology and Physiology, Northwestern University	2000
Richard P. Millman, MD	Director, Sleep Disorders Center Rhode Island Hospital	2001
Michael Rosbash, PhD	Howard Hughes Medical Institute, Department of Biology, Brandeis University	2001
David P. White, MD	Director, Sleep Disorders Program, Division of Endocrinology, Brigham and Women's Hospital	2001
Carol Landis, DNSc, RN	Department of Biology, Behavioral Nursing and Health Systems, University of Washington Seattle	2002
Emmanuel Mignot, MD, PhD	Director, Center for Narcolepsy, Stanford University School of Medicine	2002
Gene Block, PhD	Vice president and provost, University of Virginia	2004
Mary Carskadon, PhD	Professor, Department of Psychiatry and Human Behavior, Brown University School of Medicine	2004
Stuart F. Quan, MD	Chief Pulmonary and Critical Care Medicine Section Director, Sleep Disorders Center Professor of Medicine, University of Arizona	2005
Clifford Saper, MD, PhD	Professor and chair, Department of Neurology and Program in Neuroscience, Harvard Medical School	2005
Kathryn A. Lee, RN, PhD, FAAN	Professor, family health care nursing, School of Nursing, University of California, San Francisco	2006
Rafael Pelayo, MD	Assistant professor, Department of Psychiatry and Behavioral Sciences, Stanford University	2006
Susan Redline, MD, MPH	Chief, Division of Clinical Epidemiology, Department of Pediatrics, Rainbow Babies and Children's Hospital Professor of pediatrics, medicine, epidemiology, and biostatistics, Case School of Medicine	2006
Michael J. Sateia, MD	Professor of psychiatry; Director, Section of Sleep Medicine, Dartmouth University	2006
Gina Poe, PhD	Assistant professor, Department of Anesthesiology, University of Michigan Medical Center	2007
Michael H. Smolensky, PhD	Professor of environmental sciences, University of Texas-Houston	2008

continued

Name	Affiliation	Year of Term Expiration
Howard P. Roffwarg, MD	Professor of psychiatry and human behavior; Director, Division of Sleep Medicine, co-director, Animal Sleep Neurophysiology Laboratory, University of Mississippi Medical Center	2009
Phyllis C. Zee, MD, PhD	Professor of neurology, neurobiology, and physiology; director, Sleep Disorders Center, Northwestern University	2009
Public and Patient Advocates		
Carol C. Westbrook		1996
Carla G. Kidd		1998
Victoria P. Haulcy, MPH		1999
Morris L. Lyons		2000
Carol Upchurch Walker		2000
Carol Bell Anderson		2002
James Everett, Jr., MD		2002
Sandra McGinnis		2003
Dara Spearman		2003
Phillip Williams		2004
Sara Caddick, PhD		2005
Lorraine Wearley, PhD		2007
Sheila C. Connolly, RN		2007
M. Elizabeth Johns		2008
Julianne Hill		2009

NOTE: Members in bold indicate a former or the current chair of the NCSDR Advisory Board. Each term is 4 years in length.

F

National Institutes of Health Sleep-Related Initiatives: 1994–2004

TABLE F-1 Sleep Initiatives (RFAs) Sponsored by the National Institutes of Health, 1994–2004

Title	Primary Purpose	Participating Institutes/Centers	Funding Activity	Year
SCOR in Neurobiology of Sleep & Sleep Apnea: RFA-HL-96-014	Establish specialized centers of research (SCORs) programs to foster translational research.	NHLBI	P50	1996
Molecular Biology and Genetics of Sleep and Sleep Disorders: RFA-HL-96-015	Advance the understanding of the molecular and genetic basis of sleep and sleep disorders.	NHLBI, NIMH, NICHD	R01	1996
Sleep Academic Award: HL-97-015; HL-96-021	Develop and/or improve the quality of medical curricula for the prevention, management, and control of sleep disorders.	NHLBI	K07	1996, 1997
Obstructive Sleep Apnea in Children: HL-98-004	Define abnormalities in airway structure and function responsible for obstructive sleep apnea in children, and identify physiological and clinical measures associated with increased morbidity.	NHLBI, NIDR, NICHD	R01	1997
Phenotypic Characterization of Sleep in Mice: RFA-HL-99-001	Develop improved molecular, cellular, and systems approaches to investigate sleep and circadian phenotypes in mice.	NHLBI, NIMH, NIA, NINDS	R01	1998
Nocturnal Asthma, Chronobiology, and Sleep: RFA-HL-99-011	Establish the mechanisms that underlie the chronobiology of nocturnal exacerbations of asthma and airway inflammation, as well as the role played by sleep and sleep disturbances.	NHLBI	R01	1999
Implementation of the National Occupational Research Agenda: RFA-OH-99-002	Develop knowledge that can be used in preventing occupational diseases and injuries and to better understand their underlying pathophysiology.	NIOSH, NCI, NHLBI, NIA, NIDCD, NIEHS	R01, R18	1999
Data Coordinating Center for Sleep Heart Health Study: RFA-HL-99-014	Establish a new data coordinating center for the Sleep Heart Health Study.	NHLBI	U01	1999
Research on Alcohol and Sleep: RFA-AA-00-005	Stimulate research on alcohol and sleep in areas that may improve understanding of the etiology and treatment of alcoholism.	NIAAA	R01, R21	2000

Oxygen Sensing During Intermittent Hypoxia: RFA-HL-00-004	Improve understanding of how intermittent hypoxia contributes to the pathophysiology of cardiopulmonary, vascular, hematological, and sleep disorders.	NHLBI	R01	2000
Ancillary Studies in Conjunction with SHOW Trial: RFA-DK-00-017	Develop basic, clinical, and behavioral ancillary research studies of the Study of Health Outcomes of Weight-Loss (SHOW) clinical trial.	NIDDK, NHLBI, NINR, NIAMS, NIDCR	R01	2000
Interrelationships Between Sleep and Heart, Lung, and Blood Diseases: RFA-HL-01-009	Elucidate characteristics of sleep physiology, sleep disorders, and pathophysiological mechanisms mediating the interrelationships between sleep disturbance and heart, lung, and blood diseases.	NHLBI, NIDA	R01	2001
Sleep and Sleep Disorders in Children: RFA-HL-01-006	Improve the understanding of fundamental biological mechanisms through which sleep deprivation and sleep disorders affect the cardiopulmonary, hematological, immunological, mental, and behavioral health of children.	NHLBI, NIMH, NINR, NICHD	R01	2001
Role of Sleep and Sleep Disordered Breathing in the Metabolic Syndrome: RFA-HL-03-008	Elucidate the relationship of sleep deprivation and sleep-disordered breathing to characteristics of the metabolic syndrome including obesity, high blood pressure, dyslipidemia, insulin resistance, and vascular inflammation.	NHLBI, NIA	R01	2002
Inter-relationships of Sleep, Fatigue, and HIV/AIDS: RFA-HL-04-010	Elucidate the etiology of sleep disturbances and fatigue associated with human immunodeficiency virus infection and acquired immunodeficiency disease syndrome.	NHLBI, NIMH	R01	2003

NOTE: Primary purpose of each PA and RFA are adapted from language in NIH announcements. NCCAM = National Center for Complementary and Alternative Medicine; NCI = National Cancer Institute; NCSDR = National Center on Sleep Disorders Research; NHLBI = National Heart, Lung, and Blood Institute; NIA = National Institute on Aging; NIAAA = National Institute on Alcohol Abuse and Alcoholism; NIAID = National Institute of Allergy and Infectious Diseases; NIAMS = National Institute of Arthritis and Musculoskeletal and Skin Diseases; NICHD = National Institute of Child Health and Human Development; NIDA = National Institute on Drug Abuse; NIDCD = National Institute on Deafness and Other Communication Disorders; NIDCR = National Institute of Dental and Craniofacial Research; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; NIDR = National Institute of Dental Research; NIEHS = National Institute of Environmental Health Sciences; ; NIH = National Institutes of Health; NIMH = National Institute of Mental Health; NINDS = National Institute of Neurological Disorders and Stroke; NINR = National Institute of Nursing Research; NIOSH = National Institute for Occupational Safety and Health; PA = program announcement; RFA = request for application. SOURCE: National Heart, Lung, and Blood Institute, 2003; *National Sleep Disorders Research Plan*, 2003. Bethesda, MD: NIH.

TABLE F-2 Sleep Initiatives (PAs) Sponsored by the National Institutes of Health, 1994–2004

Title	Primary Purpose	Participating Institutes/Centers	Funding Activity	Year
Basic and Clinical Research on Sleep & Wakefulness: PA-95-014	Enhance sleep research in the following areas: neuroscience and behavioral science; molecular and cellular mechanisms of sleep and circadian rhythms across the life span; development of sleep from fetal life through infancy; role of dreaming in humans; etiological factors and pathophysiology of transient or persistent insomnia; and the treatment of sleep disorders.	NIA, NIAAA, NICHD, NIDA, NHLBI, NIMH, NINDS, NINR	R01, R03, R29, P01	1994
Innovative Approaches to Developing New Technologies: PA-97-014	Support research to identify, create, and develop innovative technologies and to provide these technologies for biomedical research.	NCRR	R21	1996
Research on Musculoskeletal Fitness and Sports Medicine: PA-97-025	Study a broad range of basic and clinical topics related to musculoskeletal fitness, exercise physiology, and sports medicine.	NIAMS, NICHD, NINR	R01, R03, R29, K01, K02, K08, P01	1997
Institutional National Research Service Award in Sleep Research: PA-97-064	Ensure that scientists, highly trained in sleep research, are available in adequate numbers to address important gaps in our biomedical and biological understanding of sleep, including those outlined in the NIH director's Sleep Disorders Research Plan.	NHLBI, NIA, NIAAA, NICHD, NIDA, NIMH, NINDS, NINR	T32	1997
Bioengineering Research Grants: PAR-99-009	Support basic bioengineering research whose outcomes are likely to advance health or health-related research within the mission of the NIH.	NCI, NCRR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NICHD, NIDA, NIDCD, NIMH, NINDS, NINR, NLM	R01	1998

Human Brain Project (Neuroinformatics): PAR-99-138	Encourage and support investigator-initiated, neuroinformatics research that will lead to new digital and electronic tools for all domains of neuroscience research.	NIMH, NIDA, NSF, NIA, NICHD, NIDCD, NLM, NASA, FIC, DOE, NIAAA, NHLBI, NIDCR, NCI, NINDS	R01, P01, P20	1999
Occupational Safety and Health Research: PA-99-143	Develop knowledge that can be used in preventing occupational diseases and injuries, and better understand their underlying pathophysiology.	NIOSH, NCI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NIDCD, NIEHS	R01	1999
Restless Legs Syndrome and Periodic Limb Movement Disorder: PA-01-086	Develop an understanding of the pathogenesis of RLS and PLMD that will lead to new forms of treatment.	NINDS, NHLBI, NIA, NIMH	R01	2001
Research on Sleep and Sleep Disorders: PA-05-046	Advance biomedical knowledge related to sleep or sleep disorders; improve understanding of the neurobiology or functions of sleep over the life span; enhance timely diagnosis and effective treatment for individuals affected by sleep-related disorders; or implement and evaluate innovative community-based public health education and intervention programs.	NHLBI, NCSDR, NIA, NIAAA, NIAMS, NCI, NICHD, NCCAM, NIDA, NIMH, NINDS, NINR, ORWH	R01, R21	2004

NOTE: Primary purpose of each PA and RFA are adapted from language in NIH announcements. DOE = Department of Energy; FIC = Fogarty International Center; NASA = National Aeronautics and Space Administration; NCCAM = National Center for Complementary and Alternative Medicine; NCI = National Cancer Institute; NCRR = National Center for Research Resources; NCSDR = National Center on Sleep Disorders Research; NEI = National Eye Institute; NHGRI = National Human Genome Research Institute; NHLBI = National Heart, Lung, and Blood Institute; NIA = National Institute on Aging; NIAAA = National Institute on Alcohol Abuse and Alcoholism; NIAID = National Institute of Allergy and Infectious Diseases; NIAMS = National Institute of Arthritis and Musculoskeletal and Skin Diseases; NICHD = National Institute of Child Health and Human Development; NIDA = National Institute on Drug Abuse; NIDCD = National Institute on Deafness and Other Communication Disorders; NIDCR = National Institute of Dental and Craniofacial Research; NIEHS = National Institute for Environmental Health Sciences; NIH = National Institutes of Health; NIMH = National Institute of Mental Health; NINDS = National Institute of Neurological Disorders and Stroke; NINR = National Institute of Nursing Research; NIOSH = National Institute for Occupational Safety and Health; NLM = National Library of Medicine; NSF = National Science Foundation; ORWH = Office of Research on Women's Health; PA = program announcement; RFA = request for application.

SOURCES: National Heart Lung and Blood Institute, 2003; *National Sleep Disorders Research Plan*, 2003. Bethesda, MD: NIH.

G

National Institutes of Health Support of Sleep-Related R01 Grants

The following information is a summary of extramural sleep research grants at the National Institutes of Health (NIH).

Institute of Medicine staff searched the Computer Retrieval of Information on Scientific Projects (CRISP) database for key-terms relevant to sleep. These terms include *insomnia*, *periodic limb movement disorder*, *restless legs syndrome*, *circadian rhythm*, *sudden infant death syndrome*, *sleep disorder*, *narcolepsy*, *sleep apnea*, *sleep*, *hibernation*, and *dream*. Abstracts were reviewed and only those grants with these terms listed in both the thesaurus and abstract, and not the abstract alone, were considered in the counts. The numbers for each grant reflect individual, unduplicated counts for a given year (Table G-1 and Figure G-1). All institutes were searched. Note that every abstract from 1995 and 2004 was analyzed to determine its relevance to somnology and somnopathy (see Table 6-3). This resulted in even fewer grants being relevant to the field. This analysis was not performed on grants awarded from 1996 to 2003; therefore these numbers may be slightly inflated.

TABLE G-1 Sleep-Related R01 Grants, 1995–2004

Fiscal Year	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Number of Awards	116	79	243	259	244	332	369	402	420	331
Number of New Awards	37	24	68	71	43	86	118	101	113	82

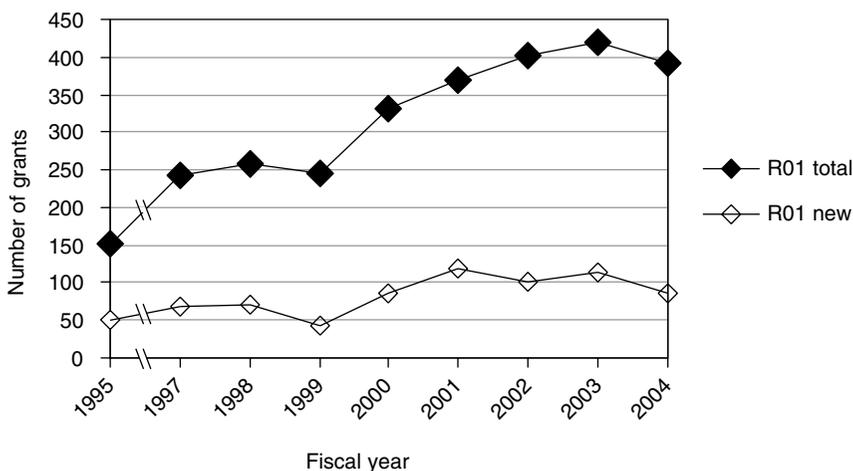


FIGURE G-1 Sleep-Related R01 Grants, 1995 to 2004.

There are 12 institutes that are members of the Trans-NIH Sleep Research Coordinating Committee. Table G-2 shows the annual NIH support of sleep-related research for various institutes. However, analysis of NIH support of sleep-related R01 grants shows that two of the largest supporters of sleep grants, the National Institute of General Medical Sciences and the National Eye Institute, are not members of the Trans-NIH Sleep Research Coordinating Committee.

TABLE G-2 Annual NIH Institute Support of Sleep-Related Research

	NIMH	NHLBI	NINDS	NIA	NIGMS	NINR	NEI	NIDA	NIAAA
1995	35	20	29	16	2	9	8	4	7
1996	26	15	14	11	0	6	0	1	1
1997	56	46	41	30	7	12	11	8	10
1998	57	47	49	32	10	10	10	11	8
1999	53	48	57	29	9	10	11	10	11
2000	72	84	59	33	10	16	14	11	9
2001	87	80	53	35	16	15	15	14	12
2002	105	93	50	40	17	15	16	17	11
2003	101	104	53	36	21	22	16	12	13
2004	88	102	49	31	22	19	15	13	12

ABBREVIATIONS: NCCAM = National Center for Complementary and Alternative Medicine; NCI = National Cancer Institute; NEI = National Eye Institute; NHLBI = National Heart, Lung, and Blood Institute; NIA = National Institute on Aging; NIAAA = National Institute on Alcohol Abuse and Alcoholism; NIAID = National Institute of Allergy and Infectious Diseases; NIAMS = National Institute of Arthritis and Musculoskeletal and Skin Diseases; NICHD = National Institute of Child Health and Human Development; NIDA = National Institute on Drug Abuse; NIDCD = National Institute on Deafness and Other Communication Disorders; NIDCR = National Institute of Dental and Craniofacial Research; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; NIGMS = National Institute of General Medical Sciences; NIH = National Institutes of Health; NIMH = National Institute of Mental Health; NINDS = National Institute of Neurological Disorders and Stroke; NINR = National Institute of Nursing Research; NIOSH = National Institute for Occupational Safety and Health.

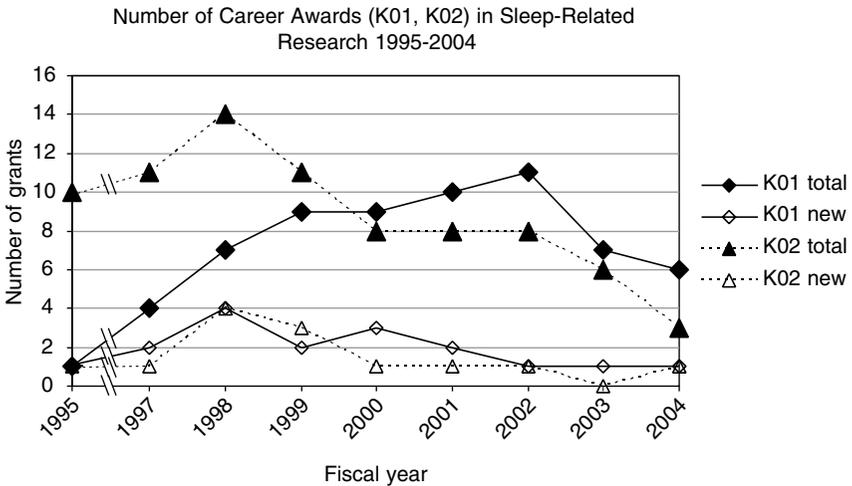
	NIDDK	NICHD	NCI	NIAMS	NIDCD	NIOSH	NCCAM	NIAID	NIDCR	FIG
	2	17	0	2	0	1	0	2	0	0
	1	6	0	0	0	0	0	1	0	0
	8	15	2	2	0	1	0	2	0	0
	8	11	2	3	0	0	0	1	1	0
	2	15	3	3	0	4	0	0	1	
	29	17	3	7	3	3	2	0	1	0
	14	17	4	7	4	3	3	0	0	0
	16	16	5	5	4	2	3	0	0	0
	15	13	6	6	3	3	4	1	0	0
	11	10	7	5	4	3	3	1	0	1

H

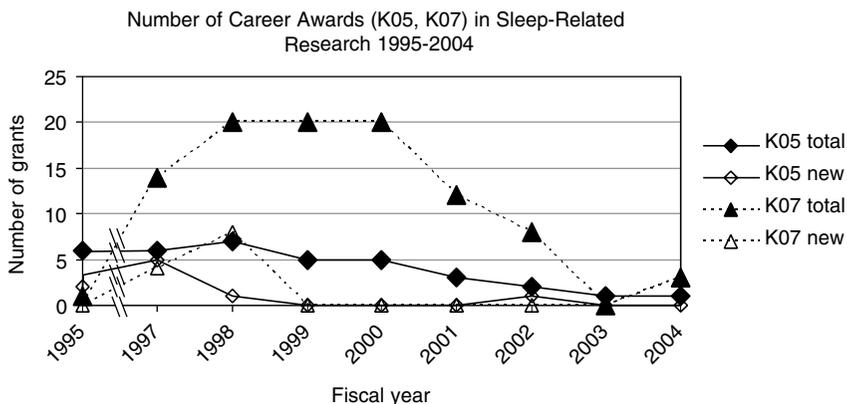
Summary of NIH Support of Sleep-Related Career Development Awards

The following information is a summary of extramural sleep research grants at the National Institutes of Health. Institute of Medicine staff searched the Computer Retrieval of Information on Scientific Projects (CRISP) database for key-terms relevant to sleep. These terms include *insomnia*, *periodic limb movement disorder*, *restless legs syndrome*, *circadian rhythm*, *sudden infant death syndrome*, *sleep disorder*, *narcolepsy*, *sleep apnea*, *sleep*, *hibernation*, and *dream*. Abstracts were reviewed and only those grants with these terms listed in both the thesaurus and abstract, and not the abstract alone, were considered in the counts. The numbers for each grant reflect individual, unduplicated counts for a given year. All institutes were searched.

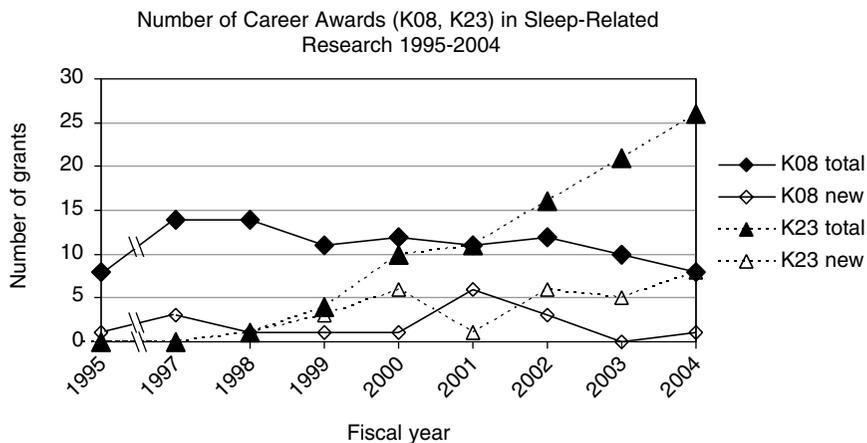
Grant	Title	Description	Number of Awards (New Awards)		
			1995	2000	2004
K01	Mentored Research Scientist Development Award	Provides salary and fringe benefits for awardees for career development experience	1 (1)	9 (3)	6 (1)
K02	Independent Scientist Award	Provides up to 5 years of salary and fringe benefit support for newly independent scientists	10 (1)	8 (1)	3 (1)



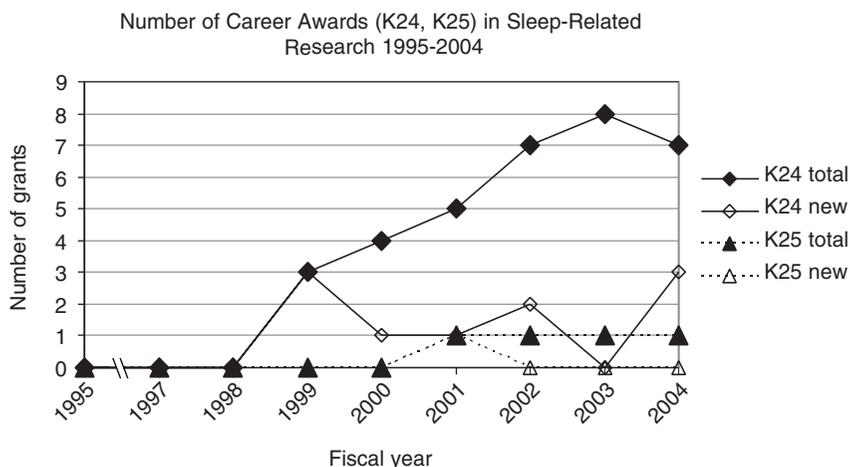
Grant	Title	Description	Number of Awards (New Awards)		
			1995	2000	2004
K05	Senior Scientist Award	Provides salary and fringe benefit support for outstanding scientists to enhance skills in their research field	6 (2)	5 (0)	1 (0)
K07	Academic	Provides up to 5 years of funding to develop or improve curricula changes that emphasize development and leadership skills of scientists	1 (0)	20 (0)	3 (3)



Grant	Title	Description	Number of Awards (New Awards)		
			1995	2000	2004
K08	Mentored Clinical Scientist Development Award	Provides salary and fringe benefit support for the development of clinician research scientists	8 (1)	12 (1)	8 (1)
K12	Mentored Clinical Scientist Development Program Award	Provides support to an educational institution for career development experiences for clinicians leading to research independence	0	0	0
K23	Mentored Patient-Oriented Research Career Development Award	Provides salary and fringe benefit support for the development of patient-oriented research scientists	0 (0)	10 (6)	28 (8)



Grant	Title	Description	Number of Awards (New Awards)		
			1995	2000	2004
K24	Midcareer Investigator Award in Patient-Oriented Research	Provides salary and fringe benefit support to allow protected time for patient-oriented research and time to act as mentors for beginning clinical investigators	0 (0)	5 (1)	8 (3)
			0 (0)	0 (0)	1 (0)
K25	Mentored Quantitative Research Career Development Award	Provides salary and fringe benefit support for career development for scientists with quantitative and engineering backgrounds to foster interdisciplinary collaboration in biomedical research			



Summary of NIH Institute Support of K Awards

Of the 314 career development awards that were funded during the 5 years between 2000 and 2004, the National Heart, Lung, and Blood Institute (NHLBI) sponsored 94 (29 percent). Thirty-two of all the NHLBI-sponsored training grants were K07 grants awarded in 2000 and 2001. K07 grants are designed to provide 5 years of funding to develop or improve curricula changes that emphasize development and leadership skills of scientists.

K01: Mentored Research Scientist Development Award

	Number of Awards (New Awards)						Total
	NIMH	NCCAM	NINR	NIA	NIDDK	NCRR	
2000	4 (1)	1 (1)	2 (1)	1 (0)	1 (0)	0 (0)	9 (3)
2001	4 (0)	1 (0)	2 (1)	1 (0)	1 (0)	1 (1)	10 (2)
2002	6 (1)	1 (0)	2 (0)	1 (0)	0 (0)	1 (0)	11 (1)
2003	3 (0)	1 (0)	1 (0)	1 (1)	0 (0)	1 (0)	7 (1)
2004	2 (0)	1 (0)	0 (0)	1 (0)	1 (1)	1 (0)	6 (1)

K02: Independent Scientist Award

	Number of Awards (New Awards)			Total
	NIMH	NINDS	NICHD	
2000	6 (1)	2 (0)	0 (0)	8 (1)
2001	6 (1)	2 (0)	0 (0)	8 (1)
2002	7 (1)	1 (0)	0 (0)	8 (1)
2003	5 (0)	1 (0)	0 (0)	6 (0)
2004	2 (0)	0 (0)	1 (1)	3 (1)

K05: Senior Scientist

	Number of Awards (New Awards)	
	NIMH	Total
2000	5 (0)	5 (0)
2001	3 (0)	3 (0)
2002	2 (1)	2 (1)
2003	1 (0)	1 (0)
2004	1 (0)	1 (0)

K07: Academic Career Award

	Number of Awards (New Awards)	
	NHLBI	Total
2000	20 (0)	20 (0)
2001	12 (0)	12 (0)
2002	8 (0)	8 (0)
2003	0 (0)	0 (0)
2004	3 (3)	3 (3)

K08: Mentored Clinical Scientist Development Award

	Number of Awards (New Awards)								Total
	NIMH	NINDS	NHLBI	NICHD	NCI	AHRQ	NEI	NIGMS	
2000	4 (1)	4 (0)	1 (0)	1 (0)	1 (0)	0 (0)	1 (0)	0 (0)	12 (1)
2001	5 (2)	3 (2)	0 (0)	1 (1)	0 (0)	0 (0)	1 (0)	1 (1)	11 (6)
2002	4 (0)	3 (1)	1 (1)	1 (0)	0 (0)	1 (1)	1 (0)	1 (0)	12 (3)
2003	4 (0)	1 (0)	1 (0)	1 (0)	0 (0)	1 (0)	1 (0)	1 (0)	10 (0)
2004	3 (0)	1 (1)	1 (0)	1 (0)	0 (0)	1 (0)	0 (0)	1 (0)	8 (1)

K23: Mentored Patient-Oriented Research Career Development Award

	Number of Awards (New Awards)							Total
	NIMH	NIA	NIDDK	NCRR	NINDS	NHLBI	NICHD	
2000	1 (1)	2 (1)	0 (0)	2 (2)	0 (0)	5 (2)	0 (0)	10 (6)
2001	1 (0)	2 (0)	0 (0)	2 (0)	0 (0)	6 (1)	0 (1)	11 (2)
2002	3 (2)	1 (0)	1 (1)	3 (1)	0 (0)	7 (1)	1 (0)	16 (5)
2003	4 (1)	1 (0)	1 (0)	4 (1)	0 (0)	9 (2)	2 (1)	21 (5)
2004	7 (2)	2 (1)	2 (1)	5 (1)	1 (1)	7 (2)	2 (0)	26 (8)

K24: Midcareer Investigator Award in Patient-Oriented Research

	Number of Awards (New Awards)						Total
	NIMH	NIAAA	NIA	NCRR	NHLBI	NICHD	
2000	1 (0)	1 (0)	1 (1)	0 (0)	1 (0)	0 (0)	4 (1)
2001	1 (0)	0 (0)	1 (0)	0 (0)	1 (0)	1 (1)	4 (1)
2002	2 (1)	1 (0)	1 (0)	0 (0)	2 (1)	1 (0)	7 (2)
2003	3 (0)	1 (0)	1 (0)	0 (0)	2 (0)	1 (0)	8 (0)
2004	1 (0)	0 (0)	1 (0)	1 (1)	3 (2)	1 (0)	7 (3)

K25: Mentored Quantitative Research

	Number of Awards (New Awards)	
	NHLBI	Total
2000	0 (0)	0 (0)
2001	0 (1)	0 (1)
2002	1 (0)	1 (0)
2003	1 (0)	1 (0)
2004	1 (0)	1 (0)

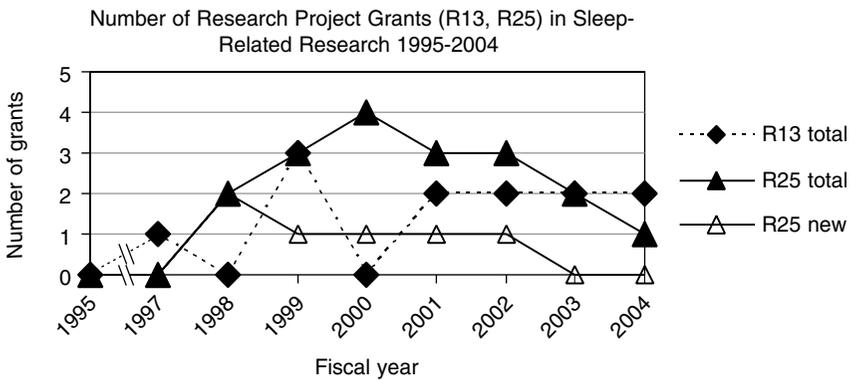
ABBREVIATIONS: AHRQ = Agency for Healthcare Research and Quality; NCCAM = National Center for Complementary and Alternative Medicine; NCI = National Cancer Institute; NCRR = National Center for Research Resources; NEI = National Eye Institute; NHLBI = National Heart, Lung, and Blood Institute; NIA = National Institute on Aging; NIAAA = National Institute on Alcohol Abuse and Alcoholism; NICHD = National Institute of Child Health and Human Development; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; NIGMS = National Institute of General Medical Sciences; NIMH = National Institute of Mental Health; NINDS = National Institute of Neurological Disorders and Stroke; NINR = National Institute of Nursing Research.

I

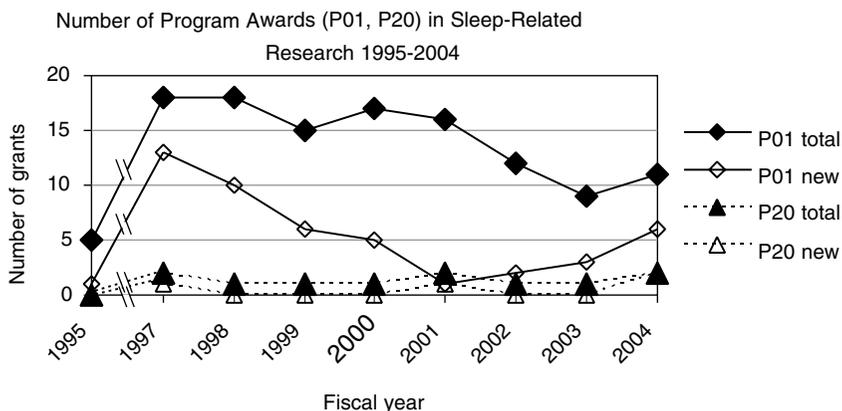
Summary of NIH Support of Sleep-Related R13, R25, P, F, T, and U Grants

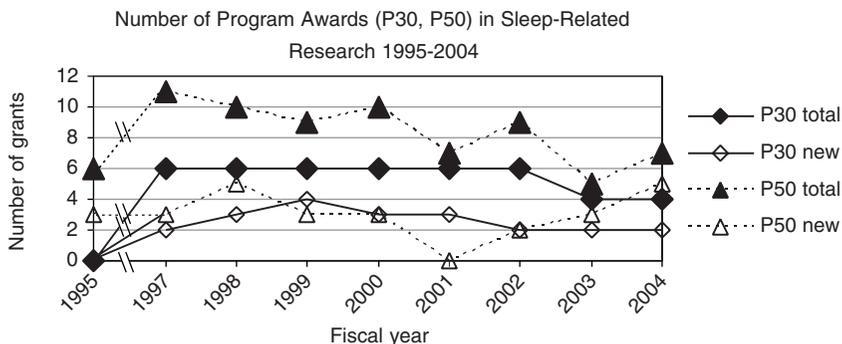
The following information is a summary of extramural sleep research grants at the National Institutes of Health. Institute of Medicine staff searched the Computer Retrieval of Information on Scientific Projects (CRISP) database for key terms relevant to sleep. These terms include *insomnia*, *periodic limb movement disorder*, *restless legs syndrome*, *circadian rhythm*, *sudden infant death syndrome*, *sleep disorder*, *narcolepsy*, *sleep apnea*, *sleep*, *hibernation*, and *dream*. Abstracts were reviewed and only those grants with these terms listed in both the thesaurus terms and abstract, not the abstract alone, were considered in the counts. The numbers for each grant reflect individual, unduplicated counts for a given year. All institutes were searched. Note that no sleep-related U grants were funded between 1994 and 2004.

Grant	Title	Description	Number of Awards (New Awards)		
			1995	2000	2004
R13	Conference Grant	Provides support for a symposium, seminar, workshop, or other formal conference assembled to exchange and disseminate information or to explore a subject, problem, or field of knowledge	0	0	2
R25	Education Project Grant	Provides support to develop a program in education, information, training, technical assistance, or evaluation	0 (0)	4 (1)	1 (0)

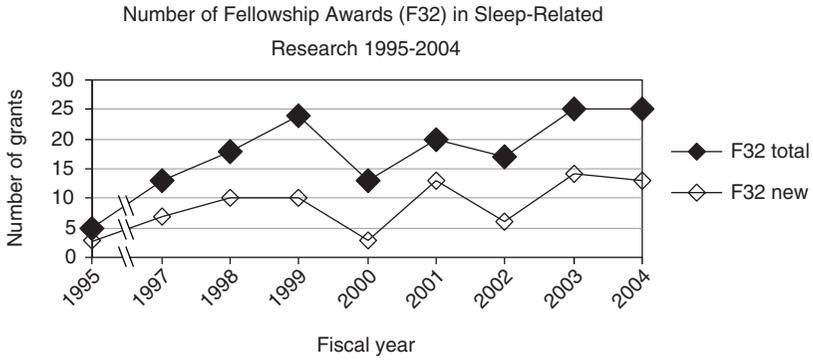
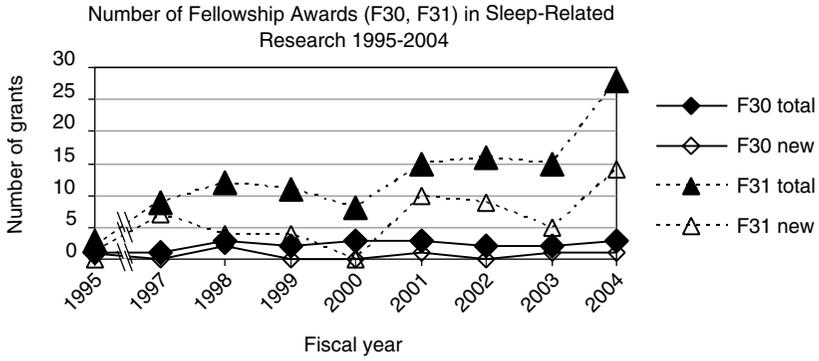


Grant	Title	Description	Number of Awards (New Awards)		
			1995	2000	2004
P01	Research Program Project	Provides support for an integrated, multiproject research program involving a number of independent investigators who share knowledge and common resources	5 (1)	17 (5)	11 (6)
P20	Exploratory Grant	Provides support for the development of new or interdisciplinary programs or the expansion of existing resources	0 (0)	1 (0)	2 (2)
P30	Center Core Grant	Provides support for shared resources and facilities to a program providing a multidisciplinary approach with existing research funds	0 (0)	6 (3)	4 (2)
P50	Specialized Center Grant	Provides support to assemble "critical masses" of basic and clinical scientists to work together collaboratively	6 (3)	10 (3)	7 (5)

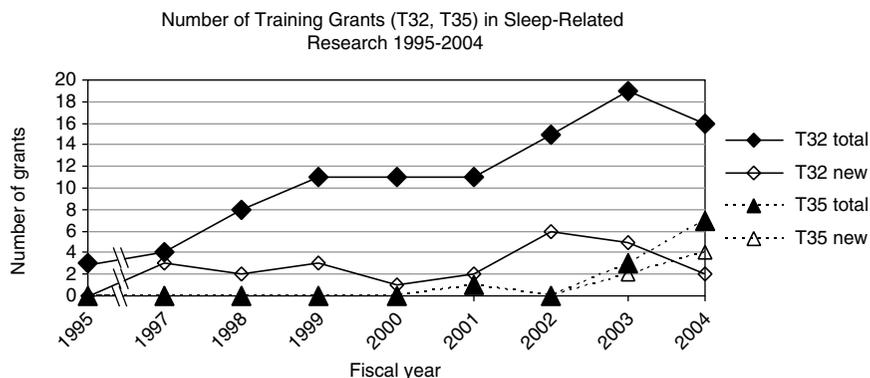




Grant	Title	Description	Number of Awards (New Awards)		
			1995	2000	2004
F30	Individual Predoctoral National Research Service Award for M.D./Ph.D. Fellowship	Fellowship award that provides combined medical school and predoctoral Ph.D. support for a maximum of 6 years	1 (1)	3 (0)	3 (1)
F31	Predoectoral Individual National Research Service Award	Fellowship award that provides up to 5 years of support for research training leading to the Ph.D. or equivalent research	3 (0)	8 (0)	28 (14)
F32	Postdoctoral Individual National Research Service Award	Fellowship award that provides postdoctoral research training to broaden scientific background	5 (3)	13 (3)	25 (13)
F33	National Research	Fellowship award that provides opportunities for experienced scientists to broaden scientific background	0	0	0



Grant	Title	Description	Number of Awards (New Awards)		
			1995	2000	2004
T32	National Research Service Award Institutional Research Training	Provides support to institutions to develop or enhance research training opportunities for predoctoral and postdoctoral students	3 (0)	11 (1)	16 (2)
T34	National Research Service Award—Undergraduate Research Training	Provides support to institutions to promote undergraduate research training to underrepresented groups in the biomedical and behavioral sciences	0	0	0
T35	Short-Term Institutional Research Training	Provides support to institutions for predoctoral and postdoctoral training focused on biomedical and behavioral research	0 (0)	0 (0)	7 (4)



J

Summary of Investment in Sleep-Related Projects at the Top 30 NIH-Funded Institutions

The following is a summary of the amount the top 30 National Institutes of Health (NIH)-funded institutions, ranked according to the total number of awards each institution received from the NIH in 2004. Institute of Medicine staff searched the Computer Retrieval of Information on Scientific Projects (CRISP) database for key-terms relevant to sleep. These terms include *insomnia, periodic limb movement disorder, restless legs syndrome, circadian rhythm, sudden infant death syndrome, sleep disorder, narcolepsy, sleep apnea, sleep, hibernation, and dream*. Abstracts were reviewed and only those grants with these terms listed in both the thesaurus terms and abstract, not the abstract alone, were considered in the counts. The committee then examined each institute's grant portfolio to determine the number of sleep-related awards it received.

TABLE J-1 Sleep-Related Research at the Top 30 NIH-Funded Institutions

Rank by Number of Total Grants	Rank by Number of Sleep Grants	Institution	Number of Awards Received
1	6	Johns Hopkins University	1,304
2	1	University of Pennsylvania	1,176
3	12	University of Washington	1,031
4	11	University of California, San Francisco	977
5	5	University of Michigan	945
6	2	University of Pittsburgh	938
7	3	University of California, Los Angeles	890
8	13	Washington University	885
9	17	Yale University	852
10	17	University of North Carolina-Chapel Hill	777
11	13	Duke University	759
12	NA ^b	Columbia University	747
13	9	Stanford University	739
14	13	Harvard University (Medical School)	723
15	18	Massachusetts General Hospital	672
16	10	Case Western Reserve University	670
17	19	University of California, San Diego	663
18	10	University of Wisconsin, Madison	653
19	10	Vanderbilt University	642
20	15	University of Minnesota	606
21	8	Emory University	580
22	19	Baylor College of Medicine	559
23	17	University of Alabama at Birmingham	553
24	2	Brigham and Women's Hospital	535
25	NA ^b	Cornell University	490
26	16	University of Colorado Denver/HSC Aurora	486
27	8	Oregon Health & Science University	473
28	11	Scripps Research Institute	465
29	12	Northwestern University	451
30	13	University of Virginia	450
Total			21,691

NOTES: To isolate only qualifying sleep-specific grants in the Total Number of Sleep Grants column, grants were obtained by searching the NIH CRISP database for key terms relevant to sleep. These terms include *insomnia*, *periodic limb movement disorder*, *restless legs syndrome*, *circadian rhythm*, *sudden infant death syndrome*, *sleep disorder*, *narcolepsy*, *sleep apnea*, *sleep*, *hibernation*, and *dream*. Abstracts were reviewed, and only those grants with these terms listed in the thesaurus were considered in the counts. The number for each institution reflects individual, unduplicated counts for a given year.

^aThe totals for P Awards are for “parent grants” and do not include subprojects.

^bColumbia and Cornell Universities both received zero sleep awards in 2004.

Number of Sleep Awards	Sleep-Related Awards				
	Number of Career Development Awards	Number of Program Awards ^a	Number of Fellowship Awards	Number of Training Awards	Number of Research Project Awards
16	3	0	2	2	9
27	7	2	2	3	13
9	1	1	1	1	5
9	1	0	3	0	5
16	0	1	0	2	13
21	4	2	2	2	11
19	2	2	1	0	14
7	0	0	2	0	5
3	0	0	0	0	3
3	0	0	1	0	2
7	0	0	0	0	7
0	0	0	0	0	0
11	0	1	0	1	9
7	1	0	1	0	5
2	1	0	1	0	0
10	3	0	0	0	7
19	2	1	2	1	13
10	0	0	1	1	8
10	1	0	0	0	9
6	1	0	0	0	5
12	0	0	3	0	9
1	0	1	0	0	0
3	0	0	0	0	3
22	6	2	3	1	10
0	0	0	0	0	0
4	0	0	0	0	4
12	2	0	0	0	10
9	0	0	3	0	6
8	0	0	2	1	5
7	1	0	1	0	5
290					

K

Biographical Sketches of Committee Members and Staff

Harvey R. Colten, M.D., (IOM) (*Chair*), recently retired as vice president and senior associate dean for Academic Affairs at Columbia University Medical Center. He was the chief medical officer, iMetrikus, Inc., and a clinical professor of pediatrics at the University of California, San Francisco, between 2000 and 2002. Previously, he served as dean of the medical school and vice president for medical affairs at Northwestern University from 1997 to 1999 and was the Harriet B. Spoehrer Professor and chair of the Department of Pediatrics at Washington University School of Medicine in St. Louis, Missouri, from 1986 to 1997. Dr. Colten earned a B.A. degree at Cornell in 1959, an M.D. from Western Reserve University in 1963, and an M.A. (honorary) from Harvard in 1978. Following his clinical training in 1965, he was an investigator at the National Institutes of Health until 1970. In 1970, he was appointed to the faculty at the Harvard Medical School, where he was named professor of pediatrics in 1979 and chief of the Division of Cell Biology, Pulmonary Medicine, and director of the Cystic Fibrosis Program at Children's Hospital Medical Center in Boston. Dr. Colten's research interests include the regulation of acute phase gene expression and genetic deficiencies of proteins that play a major role in pulmonary diseases, autoimmunity, and inflammation, on which he has published more than 270 original articles, book chapters and invited reviews. He is a member of Alpha Omega Alpha and a recipient of other honors, including a Special Faculty Research Award from Western Reserve University, the E. Mead Johnson Award for Pediatric Research, a MERIT Award from the National Institutes of Health (NIH), Distinguished Service Award from the American Association of Immunologists, and honorary membership in the Hungarian

Society of Immunology. He has been listed in Who's Who in America since 1982. Dr. Colten has been on editorial boards and advisory committees of several leading scientific and medical journals. He served on and was vice chairman of the Council of the Institute of Medicine and has served on multiple committees including the Committee on Drug Use in Food Animals, Committee on Palliative and End-of-Life Care for Children and Their Families, and the Committee for Review and Assessment of the NIH's Strategic Plan to Reduce and Ultimately Eliminate Health Disparities.

Francois M. Abboud, M.D., (IOM), is currently the Edith King Pearson Chair in Cardiovascular Research; professor of medicine, physiology, and biophysics; director, University of Iowa Cardiovascular Research Center; and associate vice president for research at the University of Iowa. He was chair of the Department of Internal Medicine from 1976 through 2002. His research is focused on integrative neurobiology of cardiovascular regulation, including the molecular determinants of sensory signaling and autonomic control. Human studies have focused on the integrated control of sympathetic activity in physiological and pathological states (e.g., sleep apnea and hypertension). He has received a number of awards, including ASPET Award for Experimental Therapeutics, American Society for Pharmacology and Experimental Therapeutics, the Wiggers Award of the American Physiological Society, the Research Achievement Award and the Gold Heart Award from the American Heart Association, and the CIBA award and medal for hypertension research of the Council for High Blood Pressure Research. He was editor-in-chief of *Circulation Research*, has served on the advisory council of the National Heart, Lung, and Blood Institute (1995–1999), is former president of the American Heart Association and the Association of American Physicians, and is currently associate editor of the journal *Physiology in Medicine*.

Gene D. Block, Ph.D., is the Thomas Jefferson Professor of Biology and the vice president and provost of the University of Virginia. Dr. Block's area of expertise is in circadian biology; he has studied the neurophysiological basis of circadian rhythms in mammals and in invertebrate models. He was founding director of the National Science Foundation's Science and Technology Center in Biological Timing. He also served as the University of Virginia's vice president for research and is past president of the Society for Research on Biological Rhythms. He received his A.B. degree from Stanford University and his Ph.D. degree from the University of Oregon.

Thomas F. Boat, M.D., (IOM), is director of the Children's Hospital Research Foundation and the professor and chair of the Department of Pediatrics at the University of Cincinnati. Dr. Boat has served as a member

and chair of the Biochemistry II Study Section of the National Institutes of Health and as a council member of the National Heart, Lung, and Blood Institute. He chairs the Research Development Program Advisory Committee for the National Cystic Fibrosis Association and is a member of their Medical Advisory Committee. Dr. Boat is a recipient of the St. Geme Award from the Federation of Pediatric Organizations as well as former chair of the American Board of Pediatrics, president of the Association of Medical School Pediatric Department Chairs, and past president of the American Pediatric Society. His areas of expertise include pathophysiology of lung disease in children, subspecialty pediatric education, improvement of health services for children, and academic health center management.

Iris F. Litt, M.D., (IOM), is the Marron and Mary Elizabeth Kendrick Professor of Pediatrics and national director of the Robert Wood Johnson Clinical Scholars Program at the Stanford University School of Medicine. Dr. Litt's research focus is on the health problems of adolescent women, with particular emphasis on the interaction of psychosocial phenomena with biological features of the second decade of life. She previously participated in multiple Institute of Medicine (IOM) committees including the Committee on Lesbian Health Research Priorities, the Committee on Youth Development, and the Forum on Adolescence, and was workshop participant on Sleep Needs, Patterns, and Difficulties of Adolescents. She has been a member of the IOM since 1995; she served as editor of the *Journal of Adolescent Health* from 1990 to 2005 and was the former director for the Division of Adolescent Medicine at Stanford University from 1976 to 2005.

Emmanuel Mignot, M.D., Ph.D., (IOM), is professor of psychiatry and behavioral sciences and director of the Center for Narcolepsy at Stanford University, as well as a Howard Hughes Medical Institute investigator. Dr. Mignot has experience in clinical and basic research in the area of sleep disorders medicine. He is board certified in sleep disorders medicine. Dr. Mignot has extensive experience in basic and clinical research of sleep disorders, most particularly with narcolepsy. He is currently on the Board of Scientific Councilors of the National Institute of Mental Health and serves on the editorial board of scientific journals in the field of sleep disorders research. Dr. Mignot is a past chair of the National Center on Sleep Disorders Research Advisory Board of the National Institutes of Health, former president of the Sleep Research Society, and former board member of the National Sleep Foundation. Dr. Mignot received both his M.D. and Ph.D. degrees from Paris University in 1984 and 1986, respectively.

Robert H. Miller, M.D., M.B.A., is the executive director of the American Board of Otolaryngology. Previously, he was professor and chair of

Otolaryngology-Head and Neck Surgery and vice chancellor at Tulane University Medical Center, dean of the University of Nevada School of Medicine, and was a Robert Wood Johnson Health Policy Fellow. His research interests have focused on the medical workforce and health policy. He received his M.D. degree in 1973 from Tulane University, did a residency in otolaryngology, performed head and neck surgery at UCLA, and received his M.B.A. degree from Tulane in 1996.

F. Javier Nieto, M.D., Ph.D., is the Helfaer Professor of Public Health, and professor and chair of the Department of Population Health Sciences at the University of Wisconsin School of Medicine and Public Health in Madison. His areas of research interest include cardiovascular disease epidemiology, markers of subclinical atherosclerosis, emerging risk factors for cardiovascular disease, and health consequences of sleep disorders and psychosocial stress. He is a board member of the American College of Epidemiology; a member of the American Society of Epidemiology; a fellow of the American Heart Association's Council on Epidemiology and Prevention; and he is affiliated with the American Public Health Association, Society for Epidemiologic Research, Spanish Epidemiologic Society, and Spanish Society of Public Health and Health Services Administration. He received his M.D. degree from University of Valencia in 1978, his M.P.H. from University of Havana, Cuba, and his Ph.D. in epidemiology from the Johns Hopkins School of Public Health in 1991.

Allan I. Pack, M.D., Ph.D., is professor of medicine and director of the Center for Sleep and Respiratory Neurobiology and chief of the Division of Sleep Medicine at the University of Pennsylvania. Dr. Pack's current major research focus is sleep and its disorders, particularly sleep apnea. In 1988, Dr. Pack was awarded one of three specialized centers of research (SCOR) in cardiopulmonary disorders during sleep from the National Institutes of Health; in 1998, he received a second SCOR in neurobiology of sleep and sleep apnea. Dr. Pack is the author of over 190 original papers and chapters and has edited three books. He has received a number of awards, including the Nathaniel Kleitman Award and the William C. Dement Academic Achievement Award from the American Academy of Sleep Medicine. He received his M.B.ChB. degree in 1968 and his Ph.D. in 1976, both from the University of Glasgow.

Kathy P. Parker, Ph.D., R.N., F.A.A.N., is the Edith F. Honeycutt Professor at the Nell Hodgson Woodruff School of Nursing and professor of neurology at Emory University. In 2001, she established the Center for Research on Symptoms, Symptom Interactions, and Health Outcomes, one of nine exploratory nursing research centers funding by the National Institute of

Nursing Research. She has more than 20 years of clinical experience in nursing and is one of five nurses in the country certified in Clinical Sleep Disorders by the American Board of Sleep Medicine. She is a fellow in the American Academy of Sleep Medicine and the American Academy of Nursing. Dr. Parker's program of research focuses on sleep-wake disturbances in hemodialysis patients and the effects of pain and opioids on sleep in cancer patients.

Samuel J. Potolicchio, M.D., is professor of neurology at the George Washington University Medical Center. Dr. Potolicchio's research interests are in sleep and convulsive disorders, particularly epilepsy, and in other neurological disorders. He also treats patients with peripheral neuropathies, sleep disturbances, mental confusion, impaired memory, and memory loss. Dr. Potolicchio has served as a member on previous Institute of Medicine Committees on the Gulf War and health.

Susan Redline, M.D., M.P.H., is professor of pediatrics, medicine, epidemiology and biostatistics at Case Western Reserve University School of Medicine and is the chief of the Division of Clinical Epidemiology in the Department of Pediatrics at Rainbow Babies & Children's Hospital. Her research interest focuses on the epidemiology of chronic diseases with an emphasis on sleep apnea, and on pulmonary and cardiovascular diseases. She directs the Case Sleep and Epidemiology Research Center, which serves as a national sleep reading center for numerous large-scale sleep epidemiological studies. Dr. Redline also directs the University Hospitals of Cleveland Sleep Disorders Center. She is an associate editor of *Sleep* and a current member of Scientific Advisory Committee of the American Thoracic Society and a member of the National Center on Sleep Disorders Research Advisory Board of the National Institutes of Health.

Charles F. Reynolds III, M.D., is a University of Pittsburgh, School of Medicine Endowed Professor of Geriatric Psychiatry, and senior associate dean of the University of Pittsburgh, School of Medicine. He directs the National Institute of Mental Health (NIMH)-sponsored Advanced Center for Interventions and Services Research in Late-Life Mood Disorders and the John A. Hartford Center of Excellence in Geriatric Psychiatry at the Western Psychiatric Institute and Clinic. Dr. Reynolds' primary research interests focus on mood and sleep disorders of later life, the prevention and treatment of those disorders, suicide prevention, and the dissemination of evidence-based practice to general medical settings. Dr. Reynolds is the past recipient of a MERIT Award and a Senior Scientist Award from the NIMH; he has led the field in studies of maintenance treatment of mood disorders in old age. He currently serves on the National Mental Health Advisory

Council and has previously served on the Institute of Medicine Committee on the Pathophysiology and Prevention of Adolescent and Adult Suicide. Dr. Reynolds is immediate past president of the American College of Psychiatrists. He graduated from the Yale University School of Medicine in 1973 and from the University of Virginia in 1969.

Clifford B. Saper, M.D., Ph.D., is James Jackson Putnam Professor of Neurology and Neuroscience at Harvard Medical School and chair of the Department of Neurology at Beth Israel Deaconess Medical Center. Previously, he was an assistant, then associate, professor in the Departments of Neurology and Anatomy and Neurobiology at the Washington University School of Medicine and associate professor and then the William D. Mabie Professor of Neurology and Neuroscience at the University of Chicago, where he chaired the graduate program in neuroscience. Dr. Saper's research interests focus on identifying neuronal circuitry involved in regulating integrated functions maintained by the hypothalamus, including wake-sleep cycles, body temperature, and feeding, and determining the homologous circuitry in human brains and examining how it may be disrupted in specific neurological and psychiatric disorders. Currently, he is editor-in-chief of the *Journal of Comparative Neurology* and serves on the editorial boards of *Neurology*, *Physiological Genomics*, *Sleep*, and *Neuroimmunomodulation*. Dr. Saper formerly was a member of the National Center on Sleep Disorders Research Advisory Board of the National Institutes of Health and previously served on the National Research Council's Howard Higher Medical Institute (HHMI) Predoctoral Fellowships Panel on Neurosciences and Physiology.

IOM STAFF

Bruce M. Altevogt, Ph.D., is a senior program officer in the Board on Health Sciences Policy at the Institute of Medicine (IOM). He received his doctoral thesis from Harvard University's Program in Neuroscience. While at Harvard Dr. Altevogt studied how the glial cells in the central and peripheral nervous system form a network of cells through intracellular communication, which is critical for maintaining myelin. After receiving his Ph.D., Dr. Altevogt was a policy fellow with the Christine Mirzayan Science & Technology Policy Graduate Fellowship Program at the National Academies. He has over 10 years of research experience. In addition to Dr. Altevogt's work at Harvard, he also performed neuroscience research at the National Institutes of Health and the University of Virginia. He received his B.A. degree from the University of Virginia in Charlottesville, where he majored in biology and minored in south Asian studies. Since joining the Board on Health Sciences Policy, he was a program officer on the IOM study *Spinal Cord*

Injury: Progress, Promise, and Priorities and is serving as the director of the Forum on Neuroscience and Nervous System Disorders and Stem Cell Research Advisory Committee.

Andrew Pope, Ph.D., is director of the Board on Health Sciences Policy at the Institute of Medicine. With a doctoral degree in physiology and biochemistry, his primary interests focus on environmental and occupational influences on human health. Dr. Pope's previous research activities focused on the neuroendocrine and reproductive effects of various environmental substances in food-producing animals. During his tenure at the National Academies and since 1989 at the Institute of Medicine, Dr. Pope has directed numerous studies; topics include injury control, disability prevention, biological markers, neurotoxicology, indoor allergens, and the enhancement of environmental and occupational health content in medical and nursing school curricula. Most recently, Dr. Pope directed studies on National Institutes of Health priority-setting processes, organ procurement and transplantation policy, and the role of science and technology in countering terrorism.

Miriam Davis, Ph.D., is an independent medical writer and consultant. She is a frequent contributor to reports of the Institute of Medicine and United States Surgeon General. After receiving her doctorate in neurobiology from Princeton University, she gained nearly 10 years of health policy experience at the Assistant Secretary for Health's office in the Department of Health and Human Services. She later became Director of Policy for the National Institutes of Health's National Institute of Environmental Health Sciences. For the past 10 years, she has been a medical writer and consultant on high-profile reports and publications and has coauthored review articles in *Science*, *Journal of the American Medical Association*, and *Neurology*. She holds an adjunct faculty post at the George Washington University School of Public Health and Health Services.

Sarah L. Hanson is a research associate in the Board on Health Sciences Policy at the Institute of Medicine. Ms. Hanson is working for the Committee on Sleep Medicine and Research. Prior to joining the Institute of Medicine, she served as research and program assistant at the National Research Center for Women & Families. Ms. Hanson has a B.A. degree from the University of Kansas with a double major in political science and international studies.

Lora K. Taylor is a senior project assistant for the Board on Health Sciences Policy working on the Sleep Medicine and Research project. She has 14 years of experience working in the academy and prior to joining the Institute of Medicine, she served as the administrative associate for the Report

Review Committee and the Division on Life Sciences' Ocean Studies Board. Ms. Taylor has a B.A. degree from Georgetown University with a double major in psychology and fine arts.

Eleanore Edson, Ph.D., a Christine Mirzayan Science & Technology Policy Graduate Fellow in the Board on Health Sciences Policy. Dr. Edson successfully defended her Ph.D. thesis in neurobiology at Harvard University in August 2005 and holds a B.S. degree in biology from Stanford University. Between college and graduate school, she studied abroad at the Glasgow School of Art on a Rotary International Scholars Fellowship.

Amy Haas is the administrative assistant for the Board on Health Sciences Policy. She previously served as a senior project assistant for the Clinical Research Roundtable. Prior to joining the Institute of Medicine, she worked as a project manager for a medical education and publishing firm in Washington, DC. She graduated from Whitman College in Walla Walla, Washington with a B.A. degree in biology.

Catharyn T. Liverman, M.L.S., is a senior program officer at the Institute of Medicine (IOM). In her 12 years at the IOM, she has worked on studies addressing a range of topics, primarily focused on public health and science policy. Most recently she was the study director for the IOM committee that produced the report *Preventing Childhood Obesity: Health in the Balance*. Other recent studies include *Testosterone and Aging: Clinical Research Directions*, *Gulf War and Health*, and *Reducing the Burden of Injury*. Her background is in medical library science, with previous positions at the National Agricultural Library and the Naval War College Library. She received a B.A. degree from Wake Forest University and an M.L.S. degree from the University of Maryland.

Kathleen M. Patchan was a research associate at the Institute of Medicine (IOM). She served as a research associate on the *Sleep Medicine and Biology* study until July 2005. She worked on a study on health literacy and assisted with staffing IOM's Sarnat Award. She also worked on an IOM study that resulted in the report *Incorporating Research into Psychiatry Residency Training*. Previously, at the Congressional Research Service and the Center on Budget and Policy Priorities, she conducted research and wrote reports on Medicaid, the State Children's Health Insurance Program (SCHIP), and state-funded immigrant health care. She has also worked at the Institute for Health Policy Solutions, where she developed reports on SCHIP and employer-sponsored health insurance. Ms. Patchan graduated from the University of Maryland at College Park with a B.S. degree in cell and molecular biology and a B.A. degree in history.

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MARIJUANA BASELINE HEALTH STUDY

FINAL REPORT | JULY 2019



MASSACHUSETTS DEPARTMENT
OF PUBLIC HEALTH
250 WASHINGTON STREET
BOSTON, MA 02108

MARIJUANA BASELINE HEALTH STUDY

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Massachusetts Department of Public Health
250 Washington Street
Boston, MA 02108
617.624.6000
www.mass.gov/dph

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Executive Summary

A legislative mandate required the Massachusetts Department of Public Health (DPH) to conduct a baseline study to investigate three topics: (1) Patterns of use, methods of consumption, and general perceptions of marijuana; (2) Incidents of impaired driving and hospitalization related to marijuana use; and (3) Economic and fiscal impacts for state and local governments. Pursuant to Section 18 of Chapter 351 of the Acts of 2016, a Report of Findings was submitted to the legislature on June 29, 2018. This document serves as the Final Report.

Summary of Findings

(1) Patterns of Use and Perceptions of Marijuana

- A survey of adults in Massachusetts suggests that approximately 21% of adults have used marijuana in the past 30 days. The proportion of marijuana use was highest among those 18-25 years old. Smoking is the most common method of marijuana consumption, although more than 40% of marijuana users report using multiple methods of use. More than half of adults perceive marijuana to have slight or no risks, and use marijuana for non-medical purposes.
- A survey of patients who use marijuana products for therapeutic use suggests these individuals use marijuana treatments for approximately 24 days a month, with the majority of respondents using a marijuana product for at least 21 out of the past 30 days. On average, respondents spend at least \$246.00 on marijuana each month, and use at least 3 different modes of use. The most common method of marijuana administration is smoking (combusting) dried flower (65%), followed by vaporizing marijuana concentrate (62%) and eating marijuana products (51%).

(2) Incidents of Impaired Driving and Hospitalization

- Tools to reliably ascertain levels of marijuana exposure and impairment in the field do not currently exist. Marijuana has cognitive and behavior effects in the areas of automative behavior (i.e., well-learned skills), and executive function impacts (i.e., how the user interacts with traffic). These effects have not been reliably linked to a level of marijuana or THC in the body.
- In a survey of Massachusetts residents, among respondents that use marijuana, the prevalence of self-reported driving under the influence is 34.3%. Overall, 7.2% of the adult population drove under the influence of marijuana in the past 30 days, and 11.3% of adults rode with a marijuana-using driver in the past 30 days. This is similar to estimates from a survey of medical marijuana patients that found approximately 10% of respondents drove under the influence in the past 30 days.

- Retrospective evaluations of fatal crash data suggest that drivers who died in a fatal crash are much more likely to have had their blood tested for marijuana, than drivers who survived a crash in which there was at least one fatality.
- Marijuana-related treatment is a small portion of the overall volume of substance use disorder treatment episodes. In a statewide-survey of Massachusetts, no respondents reported marijuana-related use of emergency room or urgent care facilities.
- The number of marijuana-related calls to the Regional Poison Control Center in Massachusetts has been increasing over time. The calls include incidents of unintentional exposures among children, with the majority of calls related to 10-19 year old individuals, and/or exposure to dried marijuana flower. The proportion of calls increased after medical marijuana was available in the Commonwealth.

(3) Economic and Fiscal Impacts for State and Local Governments

- Economic projections suggest that marijuana will increase Massachusetts state revenue by about \$215.8 million in the first two years of retail sales. The increase will largely come from sales and excise taxes collected on retail purchases. Based on experiences from states with existing legalized adult use, sales tax revenue will be higher in the second year (\$154.2 million), as compared to the first year (\$61.6 million).
- Economic projections of the impacts to local government, suggest that local tax revenue over the first two years of retail sale are projected to be highest in the most densely populated regions (ranging from \$233,498 to \$2,875,048), with considerable fluctuation in two-year revenue projections among high-density suburban cities and towns (ranging from \$68,139 to \$991,873, over the two year period).

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The MBHS was directed by DPH in consultation with an advisory panel consisting of representatives from the Executive Office of Health and Human Services, Executive Office for Administration and Finance, and the Executive Office of Public Safety and Security. The study was funded by the Medical Use of Marijuana Trust Fund.

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Specific collaborators on the “Retrospective Analysis of Indicators of Use and Perceptions of Marijuana” include: Catherine Jett, Adama Brown-Hathaway, and Penny Brierley-Bowers of the University of Massachusetts Donahue Institute.

Specific collaborators on evaluating the “Prevalence and Correlates of Marijuana Use among Adults in Massachusetts” include: Elizabeth Evans, Jennifer Whitehill, Eva Goldwater, Ed Stanek III, Penny Brierley-Bowers, and David Buchanan of the School of Public Health and Health Sciences, University of Massachusetts Amherst.

Specific collaborators evaluating the “Use and Perceptions of Marijuana among Adult Medical Use of Marijuana Patients in Massachusetts” include: Thomas W. Mangione, Natalie Spitzer, Rebecca Millock, Mihaly Imre and Heather E. Lisinski of JSI Research & Training Institute, Inc.

Specific collaborators on “Measuring Marijuana Exposure and its Effects Related to Driving Impairment: A State of the Science Review” include: Jennifer M Whitehill and Tyler Jette of the School of Public Health and Health Sciences, University of Massachusetts Amherst

Specific collaborators on evaluating “Driving Under the Influence of Marijuana and Marijuana-involved Motor Vehicle Crashes in Massachusetts” include: Jennifer M. Whitehill, Cole Fitzpatrick, Eva Goldwater, Edward Stanek III, Elizabeth Evans, and David Buchanan of the School of Public Health and Health Sciences, University of Massachusetts Amherst.

Specific collaborators on evaluating “Marijuana-Related Health System Utilization in Massachusetts” include: Jennifer M. Whitehill, Calla Harrington, and Eva Goldwater of the School of Public Health and Health Sciences, University of Massachusetts Amherst.

Specific collaborators on evaluating “Estimating Fiscal effects of Legalization in Massachusetts” include: Aparna Keshavia, Eric Morris, Dara Lee Luca, Sara Le Barron, Colleen Staatz, and David Jones of Mathematica Policy Research.

The protection of human participants in the research described in this report was ensured through review and approval by the Massachusetts Department of Public Health Institutional Review Board (IRB), and the Commissioner of Public Health pursuant to M.G.L. c.111, § 24A. For questions related to IRB or § 24A protections, please contact the Institutional Review Board at 617-624-5621 and reference the Marijuana Baseline Health Study, Principal Investigator Marc A. Nascarella, PhD, IRB# 1081301.

Introduction

A legislative mandate required the Massachusetts Department of Public Health (DPH) to conduct a baseline study to investigate three topics: (1) Patterns of use, methods of consumption, and general perceptions of marijuana; (2) Incidents of impaired driving and hospitalization related to marijuana use; and (3) Economic and fiscal impacts for state and local governments (Chapter 351 of the acts of 2016). This study, referred to as the Marijuana Baseline Health Study (MBHS), was conducted by DPH, under the leadership of the DPH Commissioner, in consultation with the Executive Office of Health and Human Services, the Executive Office for Administration and Finance, and the Executive Office of Public Safety and Security. Pursuant to the legislative mandate, DPH entered into an agreement with the following research entities to assist with the execution the study: University of Massachusetts Donahue Institute, Mathematica Policy Research Inc., and JSI Research and Training, Inc. Pursuant to Section 18 of Chapter 351 of the Acts of 2016, a Report of Findings was submitted to the legislature on June 29, 2018. This document serves as the Final Report

Topic 1: Patterns of Use and Perceptions of Marijuana

a. Retrospective Evaluation

A retrospective analysis of previous surveys of “marijuana use” was conducted by comparing national and state-specific information from three states which have legalized marijuana, compared to three states which have not. This evaluation was conducted to identify indicators which may be sensitive to factors associated with legalization of marijuana, thus providing a valuable reference to monitor trends in use and perceptions of marijuana as the legalization of marijuana progresses. This retrospective analysis suggests that thirteen different indicators from national surveys with information available at the state level appear to be responsive to factors associated with the legalization of marijuana and sensitive to changes over time. These indicators include evaluating if minors have “ever used marijuana,” and if they “believe occasional use poses no risk of harm.” The evaluation also suggests that monitoring similar indicators in adults is valuable, as well as monitoring indicators of “perceptions of great risk from smoking marijuana once a month” and “any use in the past year.”

b. Statewide Survey

A cross-sectional population-based survey of adults was conducted to assess past 30-day use of marijuana, alcohol, and other substances. For each of these three substance types, the survey collected information on frequency of use, spending on the substance, driving under the influence, riding as a passenger with a driver under the influence, and use of emergency room or urgent care services. The mail and web-based survey was designed to be representative of adults in Massachusetts, age 18 years or older. Participants were chosen randomly using address-based sampling from a list of Massachusetts residential households obtained through a sampling vendor. The sample was stratified by 6 regions (Boston, Central, Metrowest, Northwest, Southeast, and

Western). A simple random sample of 15,000 addresses were selected to participate with an equal number of households (n = 2,500) selected from each region.

Once duplicates were removed from the study results, there were 3,022 individuals that responded to the survey (21.8% response rate). The respondent data was weighted to allow estimates to be representative of the entire Massachusetts population. These weighted results suggest that 21% of adults in Massachusetts have used marijuana in the past 30 days; 26% of men and 17.0% of women. The proportion of marijuana use was highest among those 18-20 years of age and 21-25 years (54.4% and 49.1%, respectively), as compared to older age groups. Eighteen percent of adults aged 26 or older had used marijuana in the past 30 days. By region, residents in the Western area of the state report the highest prevalence of past 30-day marijuana use (~30%). Among marijuana users living in Massachusetts, most are White, 70.8%, and many fewer are Hispanic, 12.0%, Black, 7.1%, other, 6.9%, or Asian, 3.2%. In statistical analysis of the data (which accounted for the effect of other factors), race/ethnicity was not associated with marijuana use, suggesting that the likelihood of using marijuana is similar for each group (compared to Whites). Fifty-three percent of adults perceive marijuana to have slight or no risks. The patterns of marijuana consumption indicate that smoking is most common, although 43% of marijuana users report using more than just one method. More than half of all adult marijuana users (56.0%) report using marijuana only for adult non-medical purposes. Data suggest that men are more likely than women to report past 30-day use, and adults 18-20 years old are more likely to have used marijuana, compared to adults older than 26 years old. Marijuana use is positively associated with past 30-day alcohol use. Population groups such as men, White, non-Hispanic individuals and individuals age 18-20 years had the highest prevalence of marijuana use, when compared to other groups.

c. Survey of Medical Use of Marijuana Patients

An online survey of the patterns of use and perceptions of marijuana was sent to patients actively using medical marijuana. The survey remained open for approximately 5 weeks, with a stated goal of characterizing how regulated legal retail marijuana is consumed in Massachusetts. The survey included 81 questions focused on collecting information on demographics, product use, methods of use, perceptions of medical use, driving behavior, alcohol consumption, non-medical use of prescription drugs and other substances, and combined substance use.

A total of 6,934 participants completed the entire survey, for a response rate of 16%. There were no notable differences between respondent gender, age, or county of residence as compared to the eligible population (i.e., all patients). On average, respondents indicated marijuana use for 23.5 out of the past 30 days, with over 60% reporting marijuana use at least 21 out of the past 30 days. However, 8% of respondents reported no use of marijuana or marijuana products in the past 30 days. Over 65% of respondents reported using marijuana or marijuana products for medical purposes for at least 1 year, with approximately 1 in 5 of respondents using marijuana or marijuana products for medical purposes for at least 3 years. On average,

respondents reported spending \$246 on marijuana products in the past 30 days, with a significantly larger amount spent among respondents under 50 years old and among respondents with an educational attainment less than a Bachelor's degree. On average, participants reported using approximately 3 different modes of use in the past 30 days. Approximately 16% of respondents who indicated marijuana use in the past 30 days reported using only 1 method of administration, while over 30% reported using 4 or more methods. The most common method of marijuana administration was smoking dried flower (65%), followed by vaporized marijuana concentrate (62%) and edible marijuana products (51%). The amount of product used varied by gender, age group, and educational attainment. A significantly larger proportion of males compared to females reported using vaporized dried flower or a concentrated preparation of THC referred to as "dabbing", while a larger proportion of females compared to males reported using sublingual or orally administered uptake products and applying topical cannabis products to the skin. A significantly larger proportion of respondents 50 years old or younger reported smoking (combusting) dried flower cigarettes (or "joints"), vaporizing dried flower, vaporizing marijuana concentrate, dabbing, or consuming edible marijuana products. A significantly larger proportion of respondents with an educational attainment less than a Bachelor's degree reported smoking dried flower and dabbing compared to respondents with a Bachelor's degree or higher.

All respondents were asked questions related to their perceptions of the medical use of marijuana. Over 65% of respondents reported that they believed marijuana products have been "very effective" in treating their medical condition(s), while an additional 26% believed use of marijuana to be "effective." Almost 90% of respondents reported that they had "somewhat high" or "very high" confidence that they were receiving safe, uncontaminated products when purchasing marijuana or marijuana products at a registered medical marijuana dispensary. All respondents were asked questions related to positive and negative outcomes/consequences of their marijuana use. Overall, respondents reported high rates of positive outcomes/consequences of marijuana use, and little obvious harm. Among all respondents, 78% reported positive changes in their mood or mental health, and 67% reported improved physical health. In addition, 83% of respondents reported no negative outcomes/consequences related to their marijuana use. Approximately 10% of respondents reported driving or operating a car or other motor vehicle while under the influence of marijuana in the past 30 days.

Topic 2: Incidents of Impaired Driving and Hospitalization

a. Measuring Marijuana and Driving Impairment

Marijuana intoxication can impair psychomotor and cognitive functions related to driving and increase the risk of involvement in a motor vehicle crash. A literature review was conducted to examine the state of the science on quantifying marijuana and impairment leading to the inability to operate a motor vehicle. Various point-of-collection (POC) devices/kits were compared to standard analytical chemistry methods (e.g., gas chromatography mass spectrometry, or liquid chromatography- tandem mass spectrometry) to determine concentrations of $\Delta 9$ -tetrahydrocannabinol (THC), the

primary psychoactive compound in marijuana. While some of the POC devices showed a screening-level accuracy that meets or exceeds recommended standards, they are limited in their ability to serve as a diagnostic tool to indicate driving impairment. The review of studies assessing cognitive and behavioral impacts of marijuana that are relevant to driving indicate that marijuana has cognitive and behavior effects in the areas of automative behavior (i.e. well-learned skills), especially for occasional users, and there also are likely executive function impacts (i.e. how the user interacts with traffic) for some users. Additional research is needed to establish baseline levels of cannabinoids in blood, urine, and saliva, and the relationship between these levels and marijuana use. Additional data are also needed to characterize the variability in cannabinoid levels across product types and modes of consumption.

b. Baseline Assessment of Medical Use of Marijuana Patients

As a follow-up to the survey of Medical Use of Marijuana patients described above, DPH conducted a biomonitoring study to evaluate baseline levels of tetrahydrocannabinol (THC) and 1-nor-9-carboxy- Δ 9-tetrahydrocannabinol (THC-COOH) in the blood and urine of patients that were regular marijuana consumers. This study, referred to as the Baseline Assessment of Medical Marijuana Patients (BAMMP) Study, was conducted in two distinct phases. The first “recruitment” phase, involved leveraging the patient survey component of the MBHS sent to 42,519 active medical marijuana patients, and included opinion, attitude, and perception questions as well as questions specifically addressing the magnitude, frequency, type and method of marijuana use. The survey also collected data on the social and demographic characteristics of respondents, including: age, gender, race/ethnicity, employment status, income level as well as county and zip code of residence. Recruitment of BAMMP study participants from the 6,934 patient survey respondents was achieved by creating a pool of respondents that indicated an interest in participating in a follow-up research study (e.g., question No. 81 on the patient survey; see Appendix B). From this pool of 2,113 interested individuals, 333 participants were selected for follow-up for study participation based on a sampling methodology to generate a sample representative of the geography, race/ethnicity, age, and gender of the statewide population. The second “field-based” phase of the BAMMP study involved the recruitment, scheduling, and collection of detailed marijuana use information and biological specimens (e.g., blood and urine) from 134 of the 333 individuals. These field-based appointments were conducted across the state of Massachusetts, where each of the 134 participants executed a consent form, returned a completed 7-day marijuana use diary, responded to questions on a same-day questionnaire, and underwent a physical and cognitive evaluation to confirm that they were not impaired. Participants then provided clinical specimens of either urine (n = 16), or urine and blood (n = 118) for quantitative analysis of THC and THC-COOH. A full report of the BAMMP study findings are expected later this year.

c. Marijuana-Involved Motor Vehicle Crashes in Massachusetts

Baseline prevalence of self-reported DUI-marijuana and riding with a driver under the influence of marijuana (RUI-marijuana) was characterized to identify demographic risk factors associated with these behaviors. Retrospective trends and patterns of marijuana-involved motor vehicle crashes in Massachusetts were investigated between 2006 and 2016, using (1) DUI and RUI data collected as part of a statewide baseline survey of Massachusetts adults age 18 years and older; (2) Prevalence of marijuana, alcohol and drug-involved fatal crashes in Massachusetts from 2006-2016; and (3) Marijuana-involved non-fatal crashes in Massachusetts. The baseline data in Massachusetts suggests that approximately 7% of adults drove under the influence of marijuana in the past 30 days and about 12% of adults rode with a driver who was under the influence of marijuana. Nearly 35% of adults who reported marijuana use also reported DUI-marijuana, and a similar proportion reported RUI-marijuana. Retrospective evaluation of fatal crash data suggest that over the 11-year study period of 2006-2016, there were an average of 351 crashes per year in which someone died and an average of 373 traffic fatalities per year. Approximately 73% of the drivers who died in a crash were administered a post-mortem blood test. Of the deceased, blood-tested drivers, there was an increasing trend for the proportion of drivers testing positive for any cannabinoid post-mortem. In contrast, alcohol-involved crashes in Massachusetts have steadily decreased in frequency since 2006. In an examination of non-fatal crash data, an increasing number and proportion of crash reports describe marijuana. These reports preclude the accurate characterization of marijuana-involved, non-fatal crashes as the crash reports do not systematically include reporting of drug testing.

d. Marijuana-Related Health System Contacts in Massachusetts

The use of health care systems by frequent and occasional marijuana users was evaluated to determine the number and prevalence of (1) substance use treatment admissions for a primary diagnosis of cannabis use disorder; (2) emergency room and urgent care services due to marijuana, and (3) marijuana-related calls received by the regional poison control center (PCC). This phase of the study sought to provide a summary of valuable health system-related indicators from before retail sales of adult use marijuana. For this phase, three data sources were utilized for analyses. First, Massachusetts-specific data were extracted from a national substance use database to compile the number of marijuana-related treatments over 2004-2014. Second, baseline data from the statewide survey on emergency or urgent care related to marijuana use, alcohol use, and other substance use were evaluated. Finally, data from the Massachusetts and Rhode Island Regional Poison Control Center (PCC) were evaluated to characterize marijuana-related calls (for all exposure reasons) by age and year, trends in specific marijuana product type as the source of exposure (e.g. dried plant, edible preparation, etc.).

These evaluations suggest that marijuana-related treatment is a small portion of the overall volume of substance use disorder treatment episodes, with an estimated

prevalence of 45 admissions per 100,000 individuals. Of the 436 individuals who reported using marijuana in the past 30 days on the statewide-survey, no respondents reported marijuana-related use of emergency room or urgent care services in the prior year. Data from the PCC suggest that the number and proportion of marijuana-related calls has been increasing over time for all age groups. For example, during the 10-year study period (2007-2016) there were 641 calls to the PCC that involved marijuana exposure, equal to a prevalence of 9.4 calls per a 100,000 population. The evaluated calls include incidents of unintentional exposures among children age 0-9 years old (n = 27, 4.21%). The greatest number of calls were related to 10-19 year old individuals (n = 257, or 40.09%). The proportion of calls due to marijuana exposure in individual ages 0-5, 6-9, and 10-20 years old showed a statistically significant increase after medical marijuana was enacted in the Commonwealth. In all age groups, it was exposure to dried cannabis plant that resulted in the greatest number of calls to poison control, followed by edible preparations.

Topic 3: Economic and Fiscal Impacts for State and Local Governments

To evaluate the potential economic impacts on state and local government, a model was constructed to estimate the fiscal impacts during the first two years of retail sales. The model included three parts: (1) a main model, which included measures that were assumed to be major drivers of state economic impacts for which there is strong evidence to inform estimates (e.g., sales tax revenue, regulatory oversight costs and revenue, and reductions in marijuana-related law enforcement activities); (2) a supplemental model, which evaluated secondary impacts on public health, public safety, and income tax revenue for which the strength of the evidence is less definitive; and (3) a local model, which estimates local tax revenue for each city or town in Massachusetts (assuming the maximum local tax rate of 3%).

This approach suggests that marijuana will increase Massachusetts state revenue by about \$215.8 million in the first two years of retail sales. The increase will largely come from sales and excise taxes collected on retail purchases. Based on experience from states with existing legalized adult use, sales tax revenue will be higher in the second year (\$154.2 million), as compared to the first year (\$61.6 million). When measures calculated with less certainty are included in the model (because of either a lack of data or uncertain timing), the state revenue may increase by an additional \$65.3 million. Because the model includes multiple measures, the overall estimate compounds uncertainty from each of the measures. To address this, low and high ranges have been calculated. For example, the total fiscal contribution could range from \$95.7 to \$405.9 million, with two major assumptions heavily influencing the estimates. The first assumption involves the number of expected marijuana users in Massachusetts. While the model uses previous population surveys that show a prevalence of use ranging from 8.6% to 12.1%, data collected in Massachusetts suggest that it may be as high as 20.1%. When this Massachusetts-based estimate is used, revenue projections increased by 38% (from \$215.8 million to \$298.8 million). Another source of uncertainty is the changes that arise in a state when moving a regulated medical marijuana marketplace

to a combined medical and adult-use marketplace, versus changes in a state going from no sales to adult-use retail sales.

The model-based approach of estimating fiscal impacts to local government, projects that local tax revenue over the first two years of retail sale are projected to be highest in the most densely populated regions (ranging from \$233,498 to \$2,875,048), with considerable fluctuation in the two-year revenue projections in high-density suburban cities and towns (ranging from \$68,139 to \$991,873, over the two year period). These local analyses assume that approximately 65% of marijuana users would shift from purchasing their marijuana in the illicit marketplace to purchasing from a dispensary. In general, the estimated median local tax revenue over the first two years of retail sale ranges from \$72,835 in suburban communities with a low population density, to \$582,899 in urban communities with a high population density. Because these model estimates rely on the location and availability of dispensaries, each community-level estimate is dependent upon the availability of marijuana in that community and the demand for marijuana in nearby communities. For some of the 83 cities and towns included in the primary analysis, local tax revenue estimates fluctuated dramatically based on these community-level effects (for example, from about \$992,000 to \$108,000).

In general, the modeling efforts described here estimate that adult-use marijuana sales are driven primarily by the availability of dispensaries and the potential for medical marijuana dispensaries to expand and/or convert operations to include adult-use marijuana sales. The increase in revenue will largely be a result of retail purchases made by adults with heavy use (defined as consuming marijuana an average of 21 days or more each month). It is difficult to speculate what regulatory costs/benefits may have already been realized when Massachusetts implemented a medical marijuana program. For example, if revenue changes have already been realized, the assumption could be inflating some of the revenue projections by 7-28%. While it is important to consider all aspects of the fiscal impact of legalization, the estimated increase from sales and business tax revenue appear to be most significant.

Task 1: Prevalence and Perceptions of Marijuana Use

**Chapter 1: Retrospective Analysis of Indicators of Use and
Perceptions of Marijuana**

Introduction

In this chapter an exploratory, secondary data analysis of marijuana indicators using national and state-specific data from Massachusetts as well as three states which have fully legalized marijuana (Oregon, Washington, and Colorado) and three states which have made no changes to marijuana laws (Texas, Kansas, Oklahoma) is presented. The goal of the study was to identify indicators of use and perception of risk of marijuana that may be used by policymakers and program leaders to monitor the impact of the legalization of marijuana over time.

Background

During the past two decades, there have been many state policy changes with regard to marijuana use. Currently, 29 states and the District of Columbia have legalized medical marijuana and 8 states have legalized recreational marijuana. National data indicates that marijuana is the most commonly used illicit drug in the U.S. and the shifts in policy align with changes in public opinion regarding the acceptance and legality of marijuana. In addition, an increase in marijuana use prevalence and a decrease in the perceived harmfulness of marijuana use have also been noted (Hall & Kozlowski, 2015; Monte, Zane, & Heard, 2015). Recent polls show growing support for the legalization of marijuana, with some reports indicating that over 50% of Americans now view the use of marijuana as a non-moral issue (Swift, 2013; Pew Research Center, 2013). Between 2002 and 2014, marijuana use increased from 10.2% to 13.4% among adults, and the perception of harmfulness associated with marijuana use decreased from 40% to 27.8% (Swift, 2013).

Although trends in marijuana use for both adolescents and adults have been examined using national data as well as data specific to states that have legalized marijuana, few studies, if any, have conducted a comparative analyses of legalized states versus non-legalized states with regard to marijuana use (Swift, 2013; Pew Research Center, 2013; Allen & Holder, 2014; Keyes, et al. 2016). And while several studies have examined trends in marijuana use following its legalization in specific states, these trends have not been examined in relation to key policy milestones. The purpose of this study is to conduct a comparative, secondary data analysis of marijuana indicators using national and state-specific data from three legal states (Oregon, Washington, Washington) and three non-legal states (Texas, Kansas, Oklahoma). Recreational marijuana was legalized in Massachusetts in 2016, and a focal point of this study is to compare Massachusetts indicators to other states in order to identify indicators which are responsive to changes in legalization. Given changes in marijuana policies regarding recreational use, the primary purpose of this study is to identify indicators that may be sensitive to those changes and factors associated with marijuana. The data reported reflect marijuana indicators that were reported for both legal and non-legalized comparison states.

Methods

In order to identify the indicators which may be sensitive to factors associated with legalization of marijuana, a list of the most relevant potential indicators from four national data sets was detailed. This list was then honed to only those which met specific criteria for inclusion. The remaining indicators were then analyzed for responsiveness to factors associated with marijuana and change over time. In sum, the process included four steps:

1. Conduct an indicator inventory
2. Choose comparison states
3. Confirm data sources
4. Conduct statistical analyses

Along with identifying indicators that appear to be responsive to changes over time, this approach also provided a baseline for chosen indicators from which to assess future trends.

Indicator Inventory

The purpose of the inventory was to identify a comprehensive list of potential indicators and detail salient information to inform the selection of indicators for further analysis. Four data sets were selected from which to pull the comprehensive list of indicators:

- Massachusetts Youth Risk Behavior Survey (YRBS)
- Massachusetts Youth Health Survey (YHS)
- Massachusetts Behavioral Risk Factor Surveillance Survey (BRFSS)
- National Survey on Drug Use and Health (NSDUH)

Sixty-eight initial indicators were identified for consideration. From this list, indicators were chosen that met the following criteria:

- Represents population of youth and/or adults
- Availability in potential comparison states
- Sampling and weighting representative of the entire state
- Administration at regular intervals over the course of the last 10 years

The result of the prioritization was the identification of 22 indicators for further analysis.

Selection of Comparison States

The next step was to select comparison states. Two types of comparison states were selected: those that have legalized recreational marijuana and those that have not legalized nor decriminalized marijuana use. Many states have made some changes to marijuana laws either by decriminalizing, legalizing medical marijuana use, or ultimately legalizing recreational marijuana use. These changes appear to occur in a progression

and therefore our focus was to identify states on either end of the continuum. The map below (Figure 1) demonstrates the range of legalization across the United States.

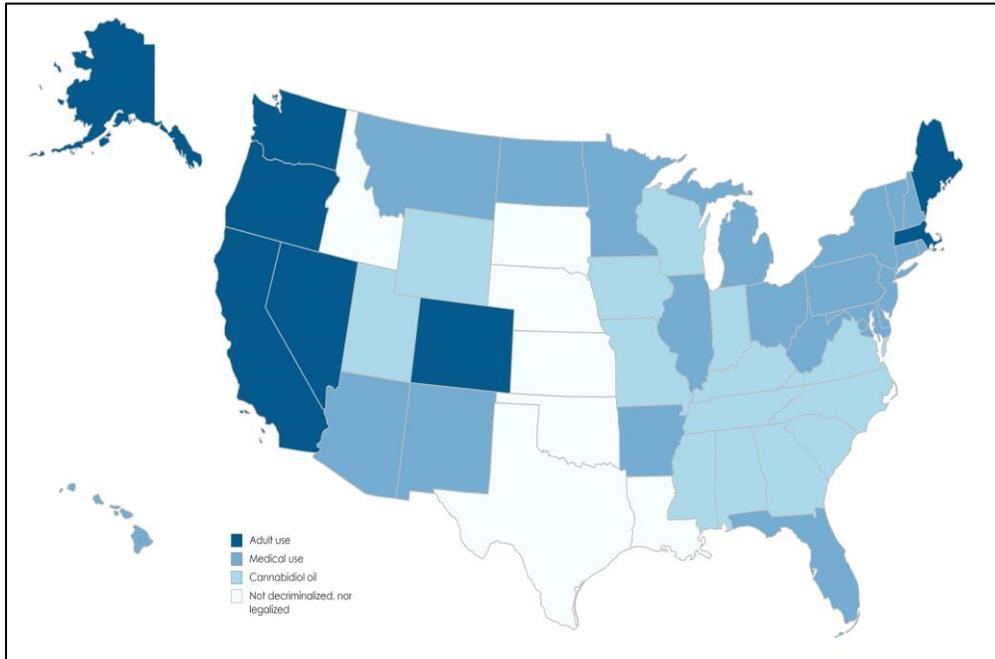


Figure 1: Current marijuana legalization status by state

For the purposes of this analysis, legalized comparison states considered included Washington, Oregon, California, Nevada, Colorado and Maine. However, only three states had legalized recreational use for sufficient time to make a trend analysis plausible: Washington, Oregon and Colorado.

A search found that there are seven states which have not decriminalized marijuana use or possession and have no recreational or medical marijuana laws, nor any legal cannabidiol oil use. These include: Idaho, Kansas, Louisiana, Nebraska, Oklahoma, South Dakota and Texas. It was assumed that states that meet this profile would be politically dissimilar (e.g. approach to criminal justice reform, social programs, etc.) from Massachusetts and therefore selecting on the basis on similarity of social factors would not be fruitful. Therefore, the selection criteria focused upon population density and unemployment rate. The table below details how each state met those criteria. Of the seven potential comparison states, the three selected had the most similar unemployment rate and population density to Massachusetts. Based on this information, the chosen non-legalization comparison states were Texas, Oklahoma and Kansas.

Table 1: Comparison State Census Information

State	Population	People per sq. mile	Unemployment rate
<i>Massachusetts</i>	6,547,629	839.4	4.3%
Idaho	1,567,582	19.0	3.1%
Kansas	2,853,118	34.9	3.7%
Nebraska	1,826,341	23.8	2.9%
Oklahoma	3,751,351	54.7	4.3%
South Dakota	814,180	10.7	3.0%
Texas	25,145,561	96.3	4.6%

Confirmation of Data Sources

Once the indicators and comparison states were chosen for analysis, the data sets were obtained. For adults, the final data sources include the NSDUH and the BRFSS. While raw NSDUH data were not available due to upgrades to SAMHSA’s online data portal and restricted data access system, a limited number of NSDUH indicators (with point estimates and confidence intervals) were available from SAMHSA’s public data access system for Massachusetts, the U.S., and all comparison states. BRFSS data regarding marijuana were only available for Washington state; other states did not include marijuana questions or included them too recently for a trend analysis to be conducted. For youth, the final data sources included the NSDUH, the YRBS, the YHS, the Healthy Youth Survey from Washington state. While the Healthy Kids Colorado Survey and the Oregon Healthy Teen Data Set were explored for use. Ultimately, they were not used due to their failing to meet the criteria set forth for the indicator inventory or their indicators did not align with Massachusetts indicators. The NSDUH data were available as described above through the public data access system for a limited number of indicators for youth aged 12-17. For high school youth, YRBS data were available for the U.S., Massachusetts, Texas, Kansas, and Oklahoma. Colorado deployed the YRBS through 2011, then switched to include the YRBS instrument in the Healthy Kids Colorado Survey, which is available for 2013 and 2015. In Washington State, the Healthy Youth Survey sampled students in grades 10 and 12; these data are not directly comparable to YRBS data but are presented on their own for trend analysis. The raw Healthy Youth Survey data were not available, but point estimates and confidence intervals available from published reports were used. For middle school youth, Massachusetts data are available from the YHS, and Washington state data are available from the Healthy Youth Survey for grades 6 and 8.

Statistical Analysis

Where raw data were available (for the YRBS, BRFSS, YHS), tests for linear and non-linear trends using logistic regression were conducted. Data were compiled and analyzed in two ways. Variables representing gender, race, and grade (in the case of youth data) were entered as control variables to adjust for demographic shifts in the underlying populations. Where raw data were not available, a significant trend was determined by non-overlapping confidence intervals; this analysis did not adjust for demographic variables. Because the sampling for each of the surveys involved complex sampling, SPSS Complex Samples version 21.0 was used to account for the sampling design and to ensure there was not an underestimation of the standard errors (Cambron, Guttmannova & Fleming, 2017).

Finally, a literature review of peer-reviewed journal articles related to marijuana legalization and block grant review was conducted to inform the selection of key milestones related to marijuana legislation in each state. Trends for each of the marijuana indicators were plotted alongside the key milestones to illustrate which indicators may be sensitive to state-level changes.

Results

The retrospective analysis resulted in identifying 13 indicators which appear to be responsive to factors associated to marijuana legalization and sensitive to change over time. Table 2 below presents a summary of the results of the analysis.

Table 2: Retrospective Analysis Results

Youth			Adult		
Indicator	Data Source	Type of Analysis	Indicator	Data Source	Type of Analysis
Ever Used Marijuana - Middle School Students	YHS	F-test, p=0.002	Ever Used Marijuana - Adults Ages 18 and Older	BRFFS	F-test, p=0.000
Used Marijuana Before Age 13 - High School Students	YRBS	F-test, p=0.005	Use in the Past Year - Adults Ages 18-25	NSDUH	State comparison, non-overlapping 95% confidence intervals
Current Marijuana Use - Middle School Students	YHS	F-test, p=0.000	Use in the Past Year - Adults Ages 26+	NSDUH	State comparison, non-overlapping 95% confidence intervals
Believe Occasional Marijuana Use Poses No Risk of Harm - High School Students	YHS	F-test, p=0.000	Current Marijuana Use - Adults Ages 18-25	NSDUH	State comparison, non-overlapping 95% confidence intervals
Believe it Would Be Easy to Obtain Marijuana - High School Students	YHS	F-test, p=0.001	Current Marijuana Use - Adults Ages 26+	NSDUH	State comparison, non-overlapping 95% confidence intervals
Perceptions of Great Risk of Smoking Marijuana Once a Month, Youth Ages 12-17	NSDUH (data not available for 2014-15)	State comparison, non-overlapping 95% confidence intervals	Perceptions of Great Risk of Smoking Marijuana Once a Month, Adults Ages 18-25	NSDUH (data not available for 2014-15)	State comparison, non-overlapping 95% confidence intervals
			Perceptions of Great Risk of Smoking Marijuana Once a Month, Adults Ages 26+	NSDUH (data not available for 2014-15)	State comparison, non-overlapping 95% confidence intervals

Indicators of Youth Marijuana Use

Marijuana use among youth has generally been stable over time, both in states that have legalized recreational marijuana use and those that have not. However, data from Massachusetts suggest that marijuana use may be declining among Massachusetts middle school aged youth. Please see Figure 2 below.

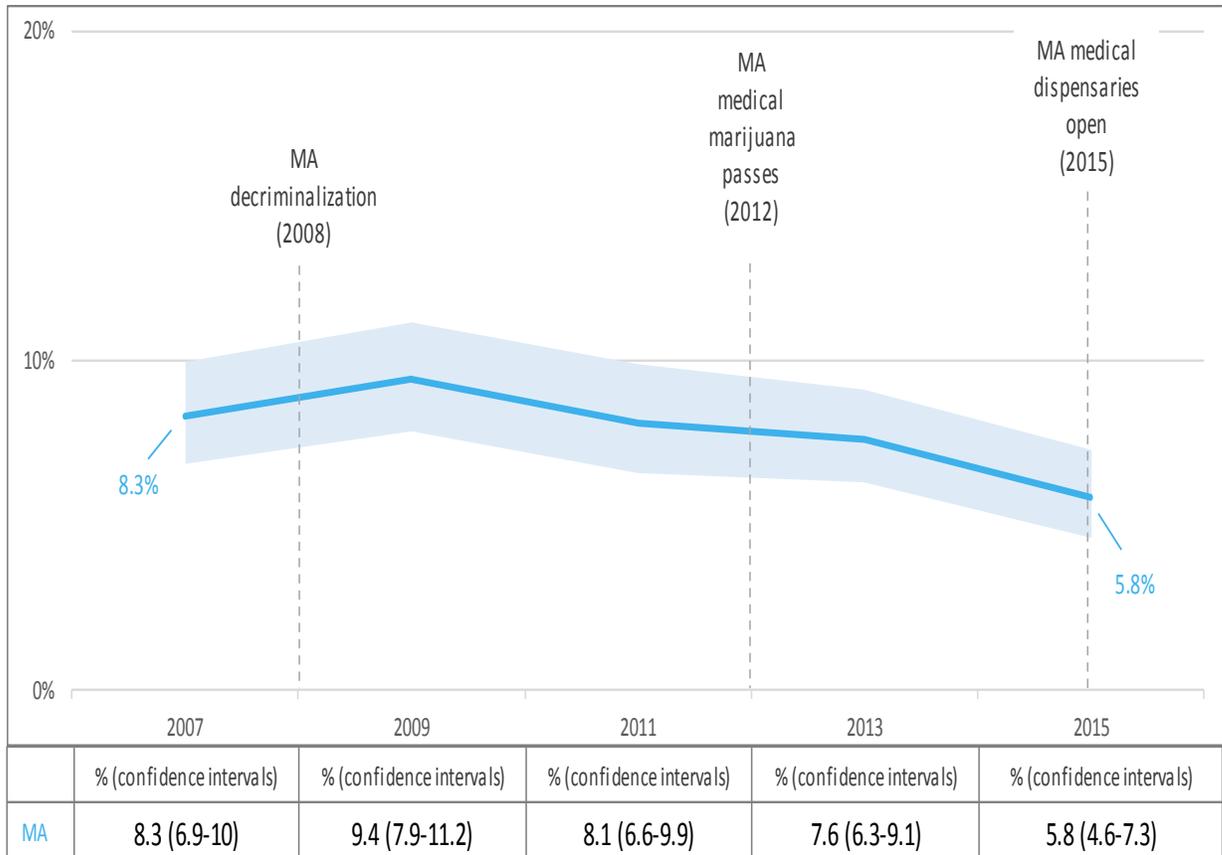


Figure 2: Massachusetts Ever Used Marijuana, Middle School Students

The specific indicators that show possible sensitivity to changes include:

- Ever Used Marijuana - Middle School Students
- Current Marijuana Use - Middle School Students
- Used Marijuana Before Age 13 - High School Students

Indicators of Youth Marijuana Perceptions

Perceptions that there is great risk in occasional marijuana use have been declining over time among youth. This trend is present in Massachusetts, nationally, and in legalized and non-legalized comparison states. More youth in non-legalized comparison states perceive that there is great risk for occasional marijuana use than youth in legalized states. Please see Figure 3 below. Massachusetts youth perceive the risk of occasional marijuana use to be lowest of all states included in analysis. In Massachusetts, this shift in perception of risk may be more pronounced in high school aged youth than in younger youth.

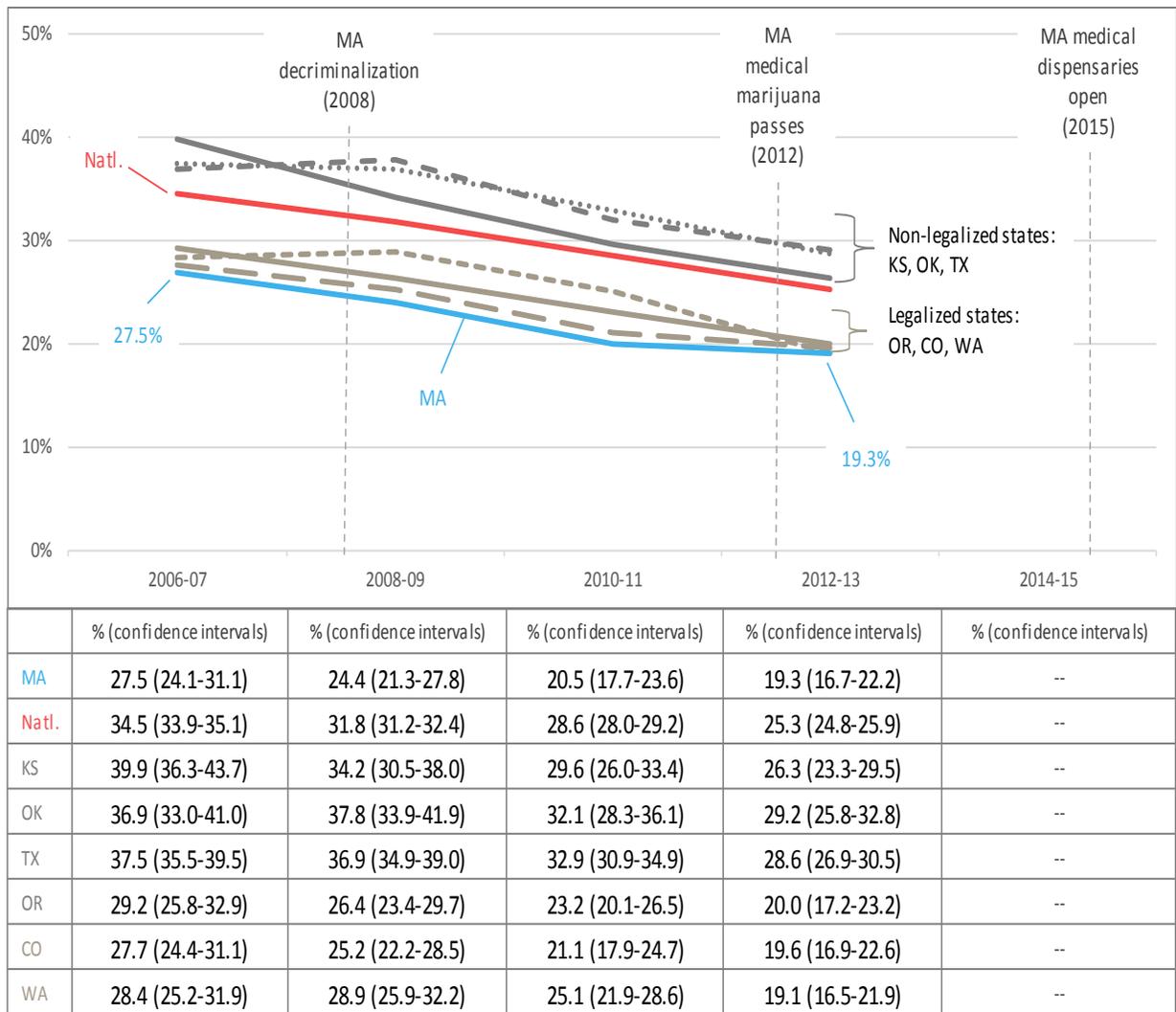


Figure 3: Massachusetts and Comparison States Perceptions of Great Risk of Smoking Marijuana Once a Month, Youth Ages 12-17

Given the parallel trends in several states, trends in these indicators may reflect larger national shifts rather than responses to state-level policy:

- Perceptions of Great Risk of Smoking Marijuana Once a Month, Youth Ages 12-17

Indicators of Adult Marijuana Use

Marijuana use seems to be increasing among some adult populations. Marijuana use among adults ages 26 and older has been increasing in Massachusetts and in states that have legalized recreational marijuana. This trend is also present nationally, though not in all non-legalized comparison states. Additionally, states that have legalized marijuana have higher rates of current use than states that do not. Finally, states that

have not legalized have rates of current use that is closer to the national average. Please see Figure 4.

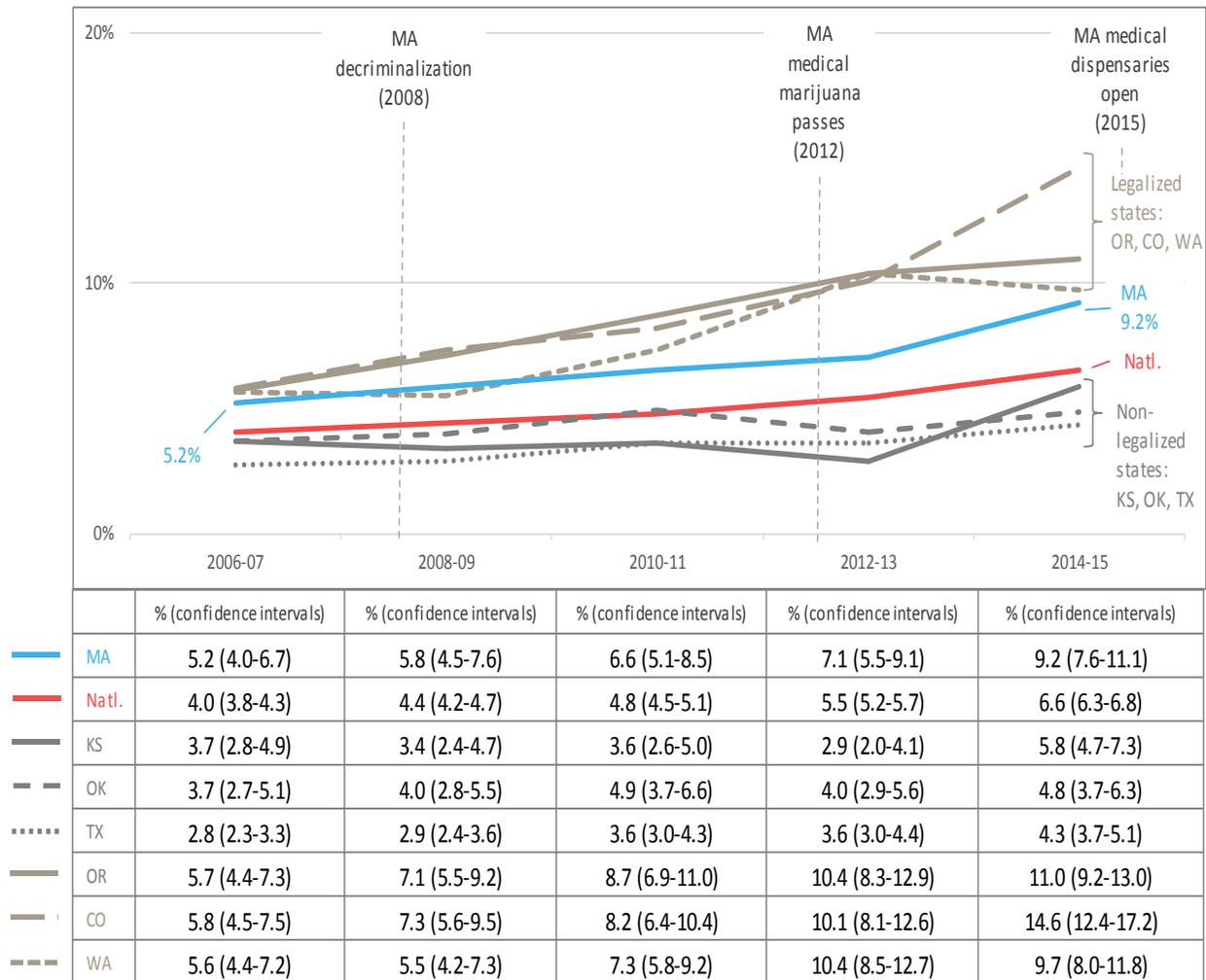


Figure 4: Massachusetts and Comparison States Current Use Ages 26 and Older

Among adults ages 18-25, who have higher rates of marijuana use than their older counterparts, use has increased in some legalized states but not in Massachusetts. Overall rates of use for all adults ages 18 and older have increased in Washington State, where recreational marijuana is legal.

The specific indicators that show possible sensitivity to policy changes include:

- Current Marijuana Use - Adults Ages 18-25 and Adults Ages 26+
- Use in the Past Year - Adults Ages 18-25 and Adults Ages 26+
- Current Marijuana Use - Adults Ages 18 and Older
- Ever Used Marijuana - Adults Ages 18 and Older

Indicators of Adult Marijuana Perceptions

As with youth, perceptions about the risks of marijuana use among adults seem to be shifting; fewer adults believe there is great risk in occasional use. This trend is occurring in Massachusetts, nationally, and in legalized and non-legalized states. Those adults in non-legalized states perceive the risk of occasional use to be higher than those in legalized states. Massachusetts adults' perceptions were closer to those in legalized comparison states than non-legalized. Please see Figures 5 and 6 below.

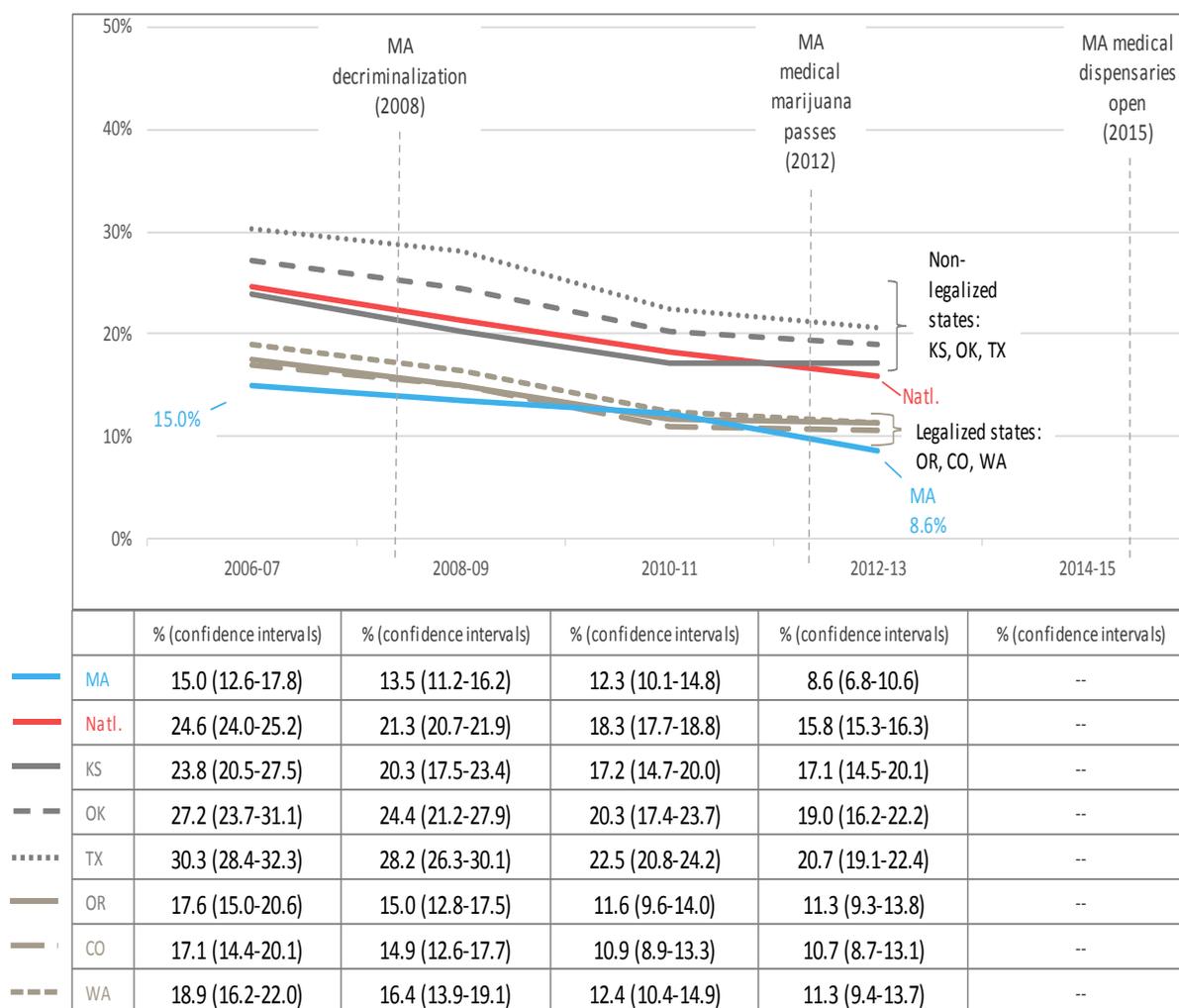


Figure 5. Massachusetts and Comparison States Perceptions of Great Risk of Smoking Marijuana Once a Month, Adults Ages 18-25

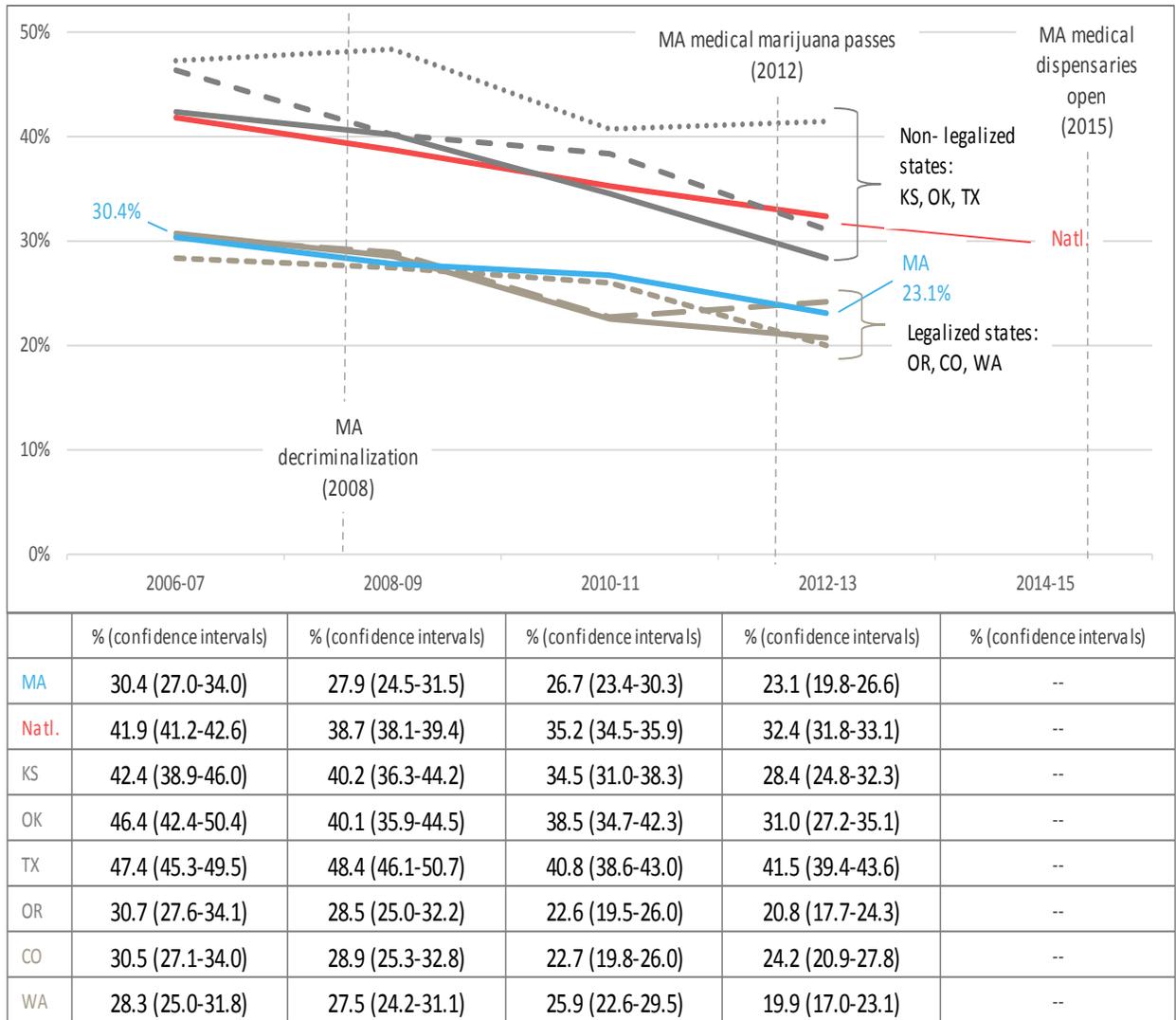


Figure 6: Massachusetts and Comparison States Perceptions of Great Risk of Smoking Marijuana Once a Month, Adults Ages 26+

Given the parallel trends in several states, trends in these indicators may reflect larger national shifts rather than responses to state-level policy:

- Perceptions of Great Risk of Smoking Marijuana Once a Month - Adults Ages 18-25 and Adults Ages 26+

Discussion

Massachusetts rates and trends consistently reflected those in comparison states that have legalized marijuana (Colorado, Oregon and Washington). And likewise legal states' trends (Kansas, Texas and Oklahoma), when comparisons were available, were different from trends in non-legal states. This suggests that some indicators may be responsive to factors associated with legalization of marijuana. The 6 indicators, 2 youth and 4 adult indicators, that differentiated between legal and non-legalized comparison states include:

- Used Marijuana Before Age 13, High School Students
- Perceptions of Great Risk of Smoking Marijuana Once a Month, Youth Ages 12-17
- Current Marijuana Use, Adults Ages 26+
- Use in the Past Year, Adults Ages 26+
- Perceptions of Great Risk of Smoking Marijuana Once a Month, Adults Ages 18-25
- Perceptions of Great Risk of Smoking Marijuana Once a Month, Adults Ages 26+

In some cases, the exact items from which the indicators are drawn, were not available for other states. For these indicators, analysis of the trends in response to policy changes was conducted. The study identified 7 indicators, 4 youth indicators and 3 adult indicators, which appear to be responsive to changes over time. These indicators include:

- Ever Used Marijuana - Middle School Students
- Current Marijuana Use - Middle School Students
- Believe Occasional Marijuana Use Poses No Risk of Harm - High School Students
- Believe it Would Be Easy to Obtain Marijuana - High School Students
- Current Marijuana Use - Adults Ages 18-25
- Use in the Past Year - Adults Ages 18-25
- Ever Used Marijuana - Adults Ages 18 and Older

One indicator, Current Marijuana Use - Adults Ages 18 and Older, was only available for Washington State and therefore it is difficult to assert that similar trends would be evident in Massachusetts. The data sets utilized were helpful when considering trends in use, consumption, and perceptions of marijuana for health and policy-related purposes. While these data are rich information, consistency with regard to the availability of the data and wording of the questions make drawing state comparisons challenging.

References

- Allen, J., & Holder, M. D. (2014). Marijuana use and well-being in university students. *Journal of Happiness Studies*, 15(2), 301–321. <https://doi.org/10.1007/s10902-013-9423-1>.
- Arria, A. M., Caldeira, K. M., O'Grady, K. E., Vincent, K. B., Fitzelle, D. B., Johnson, E. P., & Wish, E. D. (2008). Drug exposure opportunities and use patterns among college students: results of a longitudinal prospective cohort study. *Subst Abus*, 29(4), 19-38. doi: 10.1080/08897070802418451.
- Bachhuber MA, Saloner B, Cunningham CO, Barry CL. (2014) Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med*, Oct;174(10):1668-73.
- Buckner, J. D. (2013). College cannabis use: the unique roles of social norms, motives, and expectancies. *J Stud Alcohol Drugs*, 74(5), 720-726.
- Budney, A.J., Moore, B.A. (2002). Development and consequences of cannabis dependence. *Journal of Clinical Pharmacology*, 42(11 Supplement): 28S-33S.
- Cambron, C., Guttmannova, K., & Fleming, C. B. (2017). State and national contexts in evaluating cannabis laws: A case study of Washington State. *Journal of Drug Issues*, 47(1), 74–90. <https://doi.org/10.1177/0022042616678607>.
- Caulkins, J.P. (2018). The real dangers of marijuana. *National Affairs*, 35. Retrieved from <https://www.nationalaffairs.com/publications/detail/the-real-dangers-of-marijuana>.
- Chen, P., & Jacobson, K. C. (2012). Developmental trajectories of substance use from early adolescence to young adulthood: gender and racial/ethnic differences. *J Adolesc Health*, 50(2), 154-163. doi: 10.1016/j.jadohealth.2011.05.013.
- Cook, S. H., Bauermeister, J. A., Gordon-Messer, D., & Zimmerman, M. A. (2013). Online network influences on emerging adults' alcohol and drug use. *J Youth Adolesc*, 42(11), 1674-1686. doi: 10.1007/s10964-012-9869-1.
- DeWit, D. J., Offord, D. R., & Wong, M. (1997). Patterns of onset and cessation of drug use over the early part of the life course. *Health Educ Behav*, 24(6), 746-758.
- Fihn, S.D., Francis, J., Clancy, C., Nielson, C., Nelson, K., Rumsfeld, J., Cullen, T., Bates, J., Graham, G.L. (2014). Insights from advanced analytics at the Veterans Health Administration. *Health Affairs (Millwood)*, 33(7): 1203-1211.
- Gordon, A.J., Conley, J.W., Gordon, J.M. (2013). Medical consequences of marijuana use: a review of current literature. *Current Psychology Reports*, 15(12): 419.
- Halamka, J. (2007, November 12). Data, information, knowledge, and wisdom. [Web log post]. Retrieved from <http://geekdoctor.blogspot.com/2007/11/data-information-knowledge-and-wisdom.html>.
- Hall, W., Degenhardt, L. (2014). The adverse health effects of chronic cannabis use. *Drug Testing and Analysis*, 6(1-2): 39-45.
- Hall, W. & Degenhardt, L. (2009). Adverse health effects of non-medical cannabis use. *Lancet*, 374, 1383–1391.
- Hall, W. & Kozlowski, L.T. (2015). The diverging trajectories of cannabis and tobacco policies in the United States: reasons and possible implications. *Addiction*, 110(3), 241–242. <https://doi.org/10.1038/nbt.3121>.ChIP-nexus.
- Hasin DS, Sarvet AL, Cerdá M, Keyes KM, Stohl M, Galea S, Wall MM. (2017) US Adult

- Illicit Cannabis Use, Cannabis Use Disorder, and Medical Marijuana Laws: 1991-1992 to 2012-2013. *JAMA Psychiatry*, Jun 1;74(6):579-588.
- Inaba DS & Cohen WE. Uppers, downers, all arounders. Seventh Edition. CNS Productions, Inc. Medford OR.
- Kandel, D. B., & Chen, K. (2000). Types of marijuana users by longitudinal course. *J Stud Alcohol*, 61(3), 367-378.
- Keyes, K. M., Wall, M., Cerdá, M., Schulenberg, J., O'Malley, P. M., Galea, S., Hasin, D.S. (2016). How does state marijuana policy affect US youth? Medical marijuana laws, marijuana use and perceived harmfulness: 1991–2014. *Addiction*, 111(12), 2187–2195. <https://doi.org/10.1111/add.13523>.
- Longhurst, C.A., Harrington, R.A., Shah, N.H. (2014). A 'green button' for using aggregate patient data at the point of care. *Health Affairs (Millwood)*, 33(7): 1229-1235.
- Martins SS, Mauro CM, Santaella-Tenorio J, Kim JH, Cerda M, Keyes KM, Hasin DS, Galea S, Wall M. (2016). State-level medical marijuana laws, marijuana use and perceived availability of marijuana among the general U.S. population. *Drug Alcohol Depend*. Dec 1; 169:26-32.
- McCabe, S. E. (2008). Misperceptions of non-medical prescription drug use: a web survey of college students. *Addict Behav*, 33(5), 713-724. doi: 10.1016/j.addbeh.2007.12.008.
- Monte, A. A., Zane, R. D., & Heard, K. J. (2015). The implications of marijuana legalization in Colorado. *JAMA*, 313(3), 241–242. <https://doi.org/10.1038/nbt.3121.ChIP-nexus>.
- Olfson M, Wall MM, Liu SM, Blanco C. (2018). Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States. *Am J Psychiatry*. Jan 1;175(1):47-53.
- Pacula, R.L., Kilmer, B., Wagenaar, A.C., Chaloupka, F.J., Caulkins, J.P. (2014). Developing public health regulations for marijuana: lessons from alcohol and tobacco. *American Journal of Public Health*, 104(6): 1021-1028.
- Pacula, R.L., MacCoun, R., Reuter, P., Chriqui, J., Kilmer, B., Harris, K., Paoli, L., Schäfer, C. (2005). What does it mean to decriminalize marijuana? A cross-national empirical examination. *Advances in Health Economics and Health Services Research*, 16: 347-369.
- Pew Research Center. (2014). America's new drug policy landscape: Two-thirds favor treatment, not jail, for use of heroin, cocaine.
- Pischke, C. R., Zeeb, H., van Hal, G., Vriesacker, B., McAlaney, J., Bewick, B. M., . . . Mikolajczyk, R. T. (2012). A feasibility trial to examine the social norms approach for the prevention and reduction of licit and illicit drug use in European University and college students. *BMC Public Health*, 12, 882. doi: 10.1186/1471-2458-12-882.
- Powell D, Pacula RL, Jacobson M. (2018). Do medical marijuana laws reduce addictions and deaths related to pain killers? *J Health Econ*, Jan 30;58:29-42.
- Schulenberg JE, Merline AC, Johnston LD, O'Malley PM, Bachman JG, Laetz VB. (2005). Trajectories of Marijuana Use During the Transition to Adulthood: The Big Picture Based on National Panel Data. *J Drug Issues*, 35(2):255-279.
- Substance Abuse and Mental Health Services Administration. (2017). Key substance use and mental health indicators in the United States: Results from the 2016

- National Survey on Drug Use and Health (HHS Publication No. SMA 17-5044, NSDUH Series H-52). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from <https://www.samhsa.gov/data/>.
- Swift, A. (2013). For first time Americans favor legalizing marijuana. Retrieved from: www.gallup.com.
- Swift, W., Coffey, C., Degenhardt, L., Carlin, J. B., Romaniuk, H., & Patton, G. C. (2012). Cannabis and progression to other substance use in young adults: findings from a 13-year prospective population-based study. *J Epidemiol Community Health*, 66(7), e26. doi: 10.1136/jech.2010.129056.
- Tai, B., Hu, L., Ghitza, U.E., Sparenborg, S., Van Veldhuisen, P., Lindblad, R. (2014). Patient registries for substance use disorders. *Substance Abuse and Rehabilitation*, 5: 81-86.
- Tzilos, G. K., Reddy, M. K., Caviness, C. M., Anderson, B. J., & Stein, M. D. (2014). Getting higher: co-occurring drug use among marijuana-using emerging adults. *J Addict Dis*, 33(3), 202-209. doi: 10.1080/10550887.2014.950024.
- Volkow, N.D., Baler, R.D., Compton, W.M., Weiss, S.R.B. (2014). Adverse Health Effects of Marijuana Use. *The New England Journal of Medicine*, 370: 2219-2227.
- Vyas MB, LeBaron VT, Gilson AM. (2018). The use of cannabis in response to the opioid crisis: A review of the literature. *Nurs Outlook*, Jan - Feb;66(1):56-65.
- Weil, A.R. (2014). Big data in health: a new era for research and patient care. *Health Affairs (Millwood)*, 33(7): 1110.
- Zou, G. (2004). A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*, 159(7), 702-706.

Chapter 2: Prevalence and Correlates of Marijuana Use among Adults in Massachusetts

Introduction

In this Chapter, we report on prevalence of marijuana use among adults in Massachusetts, the characteristics of marijuana users compared with non-users, and the correlates of marijuana use. Findings are based on data provided by Massachusetts adults who completed a survey in the fall of 2017. Despite the existence of several ongoing surveys of Massachusetts adults, such as the Behavioral Risk Factor Surveillance Survey (BRFSS) and the National Survey on Drug Use and Health (NSDUH), there are significant gaps in the information that they provide. For example, existing Massachusetts databases did not provide information about various modes of consumption (from smoking, to eating, to vaping and dabbing).

The purpose of this survey was to address these gaps and provide a “snapshot” of marijuana use and related behaviors in Massachusetts in the time before retail sales of adult use marijuana begin. This study provides a “baseline” or benchmark against which future studies can make comparisons. The information from this survey will enable ongoing study of impacts that can inform the Commonwealth’s policy and regulatory response over the course of the next several years.

Methods

We conducted a cross-sectional, population-based survey of adults in Massachusetts. This study was approved by the Institutional Review Board at the Massachusetts Department of Public Health. A copy of the survey instrument can be found in the Appendix A.

Data Collection and Participants

The University of Massachusetts Amherst partnered with the University of Massachusetts Donahue Institute to conduct a mail and web-based survey designed to be representative of adults in Massachusetts, age 18 years or older. Participants were chosen randomly using address-based sampling from a list of Massachusetts residential households obtained through a sampling vendor. The sample was stratified by 6 regions (Boston, Central, Metrowest, Northwest, Southeast, and Western). Addresses that were known to be vacant, seasonal, educational, or drop points were excluded from the sample. A simple random sample of 15,000 addresses were selected to participate with an equal number of households (n=2500) selected from each region. The survey was then administered in four waves over a four-week period.

Wave 1: Pre-notification postcard

A pre-notification postcard was sent to selected addresses informing participants about the survey eligibility to participate. On the postcard and all subsequent mailings an online survey link with a unique access code was provided for those who chose to complete the web-based version. Online survey participants could only complete the survey once, and quality checks were implemented to identify duplicate completions (by

mail and online) using the same code. The postcard and all subsequent materials included a means to opt out of participation by calling the researchers.

Wave 2: Mail Survey

The postcard was followed by a survey packet containing an informed consent letter, the full survey, a postage-paid business reply envelope, and an up-front cash incentive of \$2. The survey instructed the adult in the household with the most recent birthday to complete the survey. Responses were tracked with a unique identification number to allow for follow-up mailings.

Wave 3: Reminder Postcard

After the initial wave of survey mailing, a reminder postcard with the online link was sent to all non-responders.

Wave 4: Final Mail Survey

The final opportunity to respond was via paper-based survey with the informed consent cover letter and online link. This was sent to those who still had not responded or had not notified the researchers of their desire not to participate.

Data were collected between November 7, 2017 (first online response opportunity) and December 30, 2017. Completed mail surveys were scanned using a computerized system. The scanned dataset was combined with the online responses and an initial quality review removed all duplicate surveys from the dataset. The resultant dataset included 3,023 respondents with a 21.7% response rate.

Measures

The survey contained 37 items that assessed a limited number of demographic characteristics, past 30-day substance use (marijuana, alcohol, and other substances), and behaviors related to substance use such as driving under the influence and riding with a driver who was under the influence. When possible the wording of items was aligned with national population health surveys (e.g. Behavioral Risk Factor Surveillance Survey, National Survey on Drug Use and Health) to facilitate comparisons of estimates.

Demographic characteristics

Basic demographics were ascertained. Participant age was ascertained by asking the survey respondent to report their year of birth. Participants reported gender as female, male, or other. Race/ethnicity was asked with two questions. One asked “Are you Hispanic or Latino?” and required a yes/no response. The second question asked “Which one or more of the following would you say is your race?” with response options that included (1) white or Caucasian, (2) Black or African American, (3) Asian, (4) Native

Hawaiian or Other Pacific Islander, (5) Native American or Alaska Native, (6) Some other race. Participants could choose as many categories as were applicable. The survey ascertained the participants' highest degree or level of school completed, which was reported on the survey with 10 categories ranging from "never attended school or only attended kindergarten" to "doctorate degree". For analysis, this was coded to a 3-level variable that included: (1) high school or less, (2) any college, (3) graduate degree. The survey asked about annual household income using the following categories (1) less than \$15,000 (2) \$15-29,000 (3) \$30,000-49,000 (4) 50,000-99,000 (5) 100,000-150,000, or (6) 150,000 or more. Participants also reported zip code as well as home ownership (own, rent, something else). Participants reported their type of healthcare coverage as one or more of the following (1) private commercial or group plan (2) Medicare, (3) Medicaid, (4) Commonwealth Care Program (Health Connector), (5) Indian Health Service (6) Veterans Affairs (7) No health insurance, or (8) other plan.

Substance Use

The survey ascertained past 30-day use of marijuana, alcohol, and other substances. Marijuana use was assessed with the yes/no question "In the past 30 days, did you use marijuana or hashish at least once?" For those who responded "yes," the survey asked about the number of days on which the participant used marijuana in the past 30 days. The purpose of marijuana use was ascertained with a multiple response item indicating use for one or more of the following: adult use (non-medical), medical use (prescribed by a qualified physician), or medical use (not prescribed by a qualified physician). The mode of use (smoking, eating, drinking, vaporizing, etc.) was assessed with a multiple response item.

Past 30-day alcohol use was reported with the yes/no question "During the past 30 days, did you have at least one drink of any alcoholic beverage such as beer, wine, a malt beverage, or liquor?" For those who responded "yes," the survey asked them to provide the number of days per week that participants consumed an alcoholic beverage. Use of other substances was coded as "Yes" if participants reported use of crack/cocaine, heroin, non-medical use of anti-anxiety drugs (sedatives, tranquilizers, anxiolytics, or sleeping drugs such as benzodiazepines or barbiturates), non-medical use of prescription opioids, or other drugs (e.g. hallucinogens, non-medical use of stimulants). The instructions to participants in the section of the survey on other substances noted that "non-medical" prescription drug use means using it to get high or experience pleasurable effects, see what the effects are like, or use with friends. Items and results pertaining to driving under the influence of marijuana, alcohol, and other drugs are reported in Task 2 of this report, along with items pertaining to use of hospital emergency rooms and urgent care related to substance use.

Data Quality Assessment

The data was subject to a quality check process. Duplicates were identified and removed, leaving 3268 respondents. We verified that skip logic was properly applied. Other instances with out-of-range responses (e.g. reported having 33 children in the home) were also coded as missing. Any instances in which returned responses were

unreasonable were coded as a missing response on the illogical variable. In cases in which a respondent reported driving under the influence of a substance, but did not first report using that substance, we set the response to the question about use to yes. This affected a very small number of cases.

Statistical Procedures and Analysis

Weighting

Weights were assigned to each completed survey so that the survey responses closely represent the Massachusetts population relative to age, gender, race, and education. The weighting scheme included six steps that are summarized below. First, a weight was assigned to directly account for the sampling fraction of addresses. Second, using information on the sample addresses, adjustments were made for unknown eligibility of the addresses. Eligibility was classified into one of four categories: (1) eligible respondent, (2) eligible non-respondent, (3) known ineligible addresses, and (4) unknown status. Eligible respondents resided at the sample address, were 18 years or older, and lived in Massachusetts for 6 or more months per year. Addresses with unknown status included addresses where surveys were not returned (n=11,163), surveys bounced back to the post office (presumably based on refusal of recipient) (n=504), and surveys returned blank (n=65). The eligibility weighting accounted for the fact that our knowledge of eligibility status may be related to other address characteristics such as the type of postal route (rural, street, firm, high-rise, etc.). The third step in the weighting was to adjust for non-response. We defined a complete survey as one in which the respondent provided basic demographics (age, gender, race, and education) and answered the item on past 30-day marijuana use. We observed a difference in the survey completion rate for eligible addresses by region ($p=0.03$) and a weight was developed to account for this. Household size was accounted for next.

Raking was then used to align the weights to the distribution of four demographic variables (age, gender, race/ethnicity, and education) to the Massachusetts target population based on the 2016 American Community Survey Public Use Microdata Sample (PUMS) data. The last step trimmed weights to improve estimation accuracy.

Statistical Analysis

In most cases, variables were defined as shown on the survey. For example, past 30-day marijuana use was defined as “Yes” based on an answer of yes to the question, “In the past 30 days, did you use marijuana or hashish at least once?” For analysis purposes, we coded race as a 5-level categorical variable with the following categories (1) White, non-Hispanic, (2) Black non-Hispanic, (3) Any Hispanic/Latino (4) Asian, non-Hispanic, (5) Other.

First, we examined the bivariate differences in characteristics between adults who had used marijuana in the past 30 days and those who had not. Next, we used modified

Poisson regression with robust standard errors (Zou, 2004) to assess associations between use of marijuana (yes/no), gender, age, race/ethnicity, and other covariates (education, home ownership, children in household, region, alcohol and other substance use). This approach allowed estimation of relative risk, adjusting for potential confounders. We used a two-tailed significance level at $p < 0.05$ for all statistical tests. All analyses were weighted to account for the complex survey design, yielding results that have been adjusted to be representative of the adult population in Massachusetts. The analysis for this report was generated using SAS/STAT software, Version 9.4 of the SAS System for Windows (Copyright © 2016 SAS Institute Inc. Cary, NC, USA.) with the exception of the Poisson regression models which were generated using Stata 15 statistical software (StataCorp, LLC, College Station, TX).

Results

A total of 3,528 surveys were returned, of which 260 were duplicates. And additional 245 were determined ineligible or incomplete. After removing the duplicate, ineligible and complete surveys, 3,023 remained. The logic-checking process resulted in identification of one case in which multiple questions had unreasonable responses. This case was dropped, resulting in a final analytic sample of 3,022.

Prevalence of Marijuana Use

Of the 3,022 adults in the sample, 439 self-reported marijuana use in the past 30 days, and 2,583 did not. After data were weighted, results indicate that 21.1% of adults in Massachusetts have used marijuana in the past 30 days (95% Confidence Interval [CI] 18.6, 23.6), and 78.9% have not (95% CI 76.4, 81.4) (Table 1). Hereafter, we report only the population-level point estimates; confidence interval data are presented in each table.

We examined prevalence rates of past 30-day marijuana use among key socio-demographic groups. These analyses indicated that 25.9% of adult men in Massachusetts and 17.0% of women have used marijuana in the past 30 days. By age category, past 30-day marijuana use was reported by 54.4% of adults aged 18 to 20, 49.1% of those aged 21 to 25, 34.5% of those aged 26 to 29, 22.7% of those aged 30 to 39, 19.3% of those aged 40 to 49, 18.7% of those aged 50 to 59, 14.1% of those aged 60 to 69, and 3.4% of those aged 70 or older. To enable comparisons of age-specific marijuana prevalence with other estimates (presented in Chapter 1), we changed the categorization of age to create a category that captured aged 26 or older. Past 30-day marijuana use was reported by 18.0% (95% CI 15.7, 20.3) of adults aged 26 or older. By race/ethnicity, past 30-day marijuana use was reported by 20.1% of Whites, 27.1% of Hispanics, 10.4% of Asians, 25.8% of Blacks, and 37.5% of other race/ethnic groups. By educational attainment, past 30-day marijuana use was reported by 24.7% of adults with a High School education or less, 22.9% of those with a college degree, and 10.7% of adults with a post-secondary graduate degree. By income, past 30-day marijuana use was reported by 32.5% of adults earning less than \$15,000. Fewer people in each of the higher income categories reported past 30-day use, with

prevalence rates ranging between about 17.3% and 25%. By region, past 30-day marijuana use was reported by 29.8% of Western residents, 20.9% of Southeast residents, 20.5% of Boston residents, 20.1% of Northeast residents, 19.6% of Central residents, and 18.2% of Metrowest residents.

Socio-Demographic Characteristics

Table 2 presents socio-demographic characteristics of adults who had used marijuana in the past 30 days compared with adults who had not. A greater proportion of marijuana users than non-users are men, 57.7% versus 44.5% ($p < 0.001$). With respect to age, marijuana users tend to be younger than non-users, with a greater proportion of them in the youngest age categories ($p < 0.001$). Specifically, 9.6% of marijuana users are aged 18 to 20, versus 2.2% of non-users, 14.7% of marijuana users are 21 to 25, versus 4.2% of non-users, and 14.3% of marijuana users are 26 to 29, versus 7.4% of non-users. For the 30 to 59 age categories, differences between marijuana users and non-users are small ($< 5\%$). A smaller proportion of marijuana users than non-users are aged 60 to 69, 10.1% versus 16.7%, and a smaller proportion are 70 or older, 2.3% versus 17.2%.

A smaller proportion of marijuana users than non-users are White or Asian, and a greater proportion are Hispanic, African American, or other race/ethnicity ($p < 0.05$). Specifically, 70.8% of marijuana users are White, versus 75.5% of non-users, and 3.2% of marijuana users are Asian, versus 7.3% of non-users. Among marijuana users, 12.0% are Hispanic, 7.1% are African American, and 6.9% are another race/ethnicity. Among non-users, in comparison, 8.7% are Hispanic, 5.5% are African American, and 3.1% are another race/ethnicity.

Table 1. Prevalence Rate of Past 30-day Marijuana Use by Key Socio - Demographic Characteristics

	%	95% CI	
Total population	21.1	18.6	23.6
Gender			
Female	17.0	14.1	20.0
Male	25.9	21.9	29.9
Age			
18-20	54.4	32.3	76.4
21-25	49.1	35.1	63.1
26-29	34.5	23.6	45.5
30-39	22.7	16.7	28.7
40-49	19.3	12.8	25.8
50=59	18.7	14.9	22.5
60-69	14.1	10.4	17.8
>=70	3.4	1.0	5.9
Race/Ethnicity			
White, non-Hispanic	20.1	17.5	22.8
Hispanic	27.1	16.7	37.5
Asian, non-Hispanic	10.4	2.7	18.2
Black, non-Hispanic	25.8	12.1	39.5
Other, non-Hispanic	37.4	21.9	52.9
Education			
<=HS	24.7	19.1	30.3
College	22.9	19.6	26.1
Graduate degree	10.7	7.9	13.4
Income			
Less than \$15,000	32.5	22.7	42.4
\$15,000 - \$29,999	24.6	16.2	33.1
\$30,000 - \$49,999	17.3	11.2	23.4
\$50,000 - \$99,999	20.7	16.0	25.4
\$100,000 - \$149,999	21.5	15.7	27.3
\$150,000 or more	19.8	13.9	25.7
Region			
Boston	20.5	13.8	27.2
Central	19.6	14.0	25.3
Metrowest	18.2	12.6	23.7
Northeast	20.1	14.6	25.7
Southeast	20.9	14.7	27.2
Western	29.8	23.2	36.4

A greater proportion of marijuana users than non-users have attained a High School diploma or college degree, and a smaller proportion have attained a graduate degree ($p<0.001$). A smaller proportion of marijuana users than non-users own a home, and a greater proportion rent or have another type of living arrangements ($p<0.001$).

There are no differences between marijuana users and non-users in the remaining socio-demographic characteristics, including income, having children in the home, health insurance type, and region of residence. For both groups, most report an income of \$50,000 to \$99,999 or more, few have children in the home, private health insurance is the most common type of health insurance, followed by Medicare and Mass Health.

Table 2. Socio-Demographic Characteristics of Marijuana Users and Non-Users

	In the past 30 days, did you use marijuana or hashish at least once?								
	Yes: n=439, 21.1% (95% CI 18.6, 23.6)			No: n=2,583, 78.9% (95% CI 76.4, 81.4)			Total: n=3,022		
	%	95% CI		%	95% CI		%	95% CI	
Gender***									
Female	42.3	35.6	48.9	55.5	52.7	58.4	52.7	50.0	55.4
Male	57.7	51.1	64.4	44.5	41.6	47.3	47.3	44.6	50.0
Age***									
18-20	9.6	4.2	15.0	2.2	0.8	3.6	3.8	2.1	5.4
21-25	14.7	9.5	20.0	4.2	2.5	5.8	6.4	4.7	8.1
26-29	14.3	9.1	19.6	7.4	5.5	9.2	8.9	7.0	10.7
30-39	18.1	13.1	23.2	16.8	14.4	19.1	17.0	14.9	19.2
40-49	15.5	10.0	20.9	17.6	15.2	19.9	17.1	15.0	19.3
50-59	15.3	11.8	18.9	18.0	16.1	19.9	17.5	15.8	19.1
60-69	10.1	7.2	13.1	16.7	15.0	18.4	15.3	13.8	16.8
>=70	2.3	0.6	3.9	17.2	15.5	18.9	14.0	12.6	15.4
Race/Ethnicity*									
White, non-Hispanic	70.8	64.0	77.7	75.4	72.6	78.3	74.5	71.8	77.1
Hispanic	12.0	7.0	16.9	8.7	6.4	10.9	9.4	7.3	11.4
Asian, non-Hispanic	3.2	0.7	5.7	7.3	5.6	9.0	6.4	5.0	7.8
Black, non-Hispanic	7.1	2.7	11.6	5.5	4.0	7.0	5.8	4.3	7.4
Other, non-Hispanic	6.9	3.1	10.7	3.1	2.1	4.1	3.9	2.8	5.0
Education***									
<=HS	38.4	31.1	45.7	31.9	28.8	34.9	33.2	30.4	36.1
College	53.1	46.1	60.1	48.8	45.9	51.6	49.7	47.0	52.4
Graduate degree	8.5	6.1	10.9	19.4	17.6	21.1	17.1	15.5	18.6
Income									
Less than \$15,000	15.9	10.3	21.4	9.2	7.2	11.1	10.6	8.7	12.6
\$15,000 - \$29,999	11.2	6.9	15.6	9.6	7.8	11.3	9.9	8.2	11.6
\$30,000 - \$49,999	12.7	8.0	17.4	16.9	14.5	19.3	16.0	13.8	18.1
\$50,000 - \$99,999	27.3	21.1	33.6	29.2	26.6	31.7	28.8	26.4	31.2
\$100,000 - \$149,999	17.5	12.5	22.6	17.8	15.6	20.1	17.8	15.7	19.9
\$150,000 or more	15.4	10.4	20.4	17.4	15.4	19.3	16.9	15.1	18.8

(Continued) Table 2. Socio-Demographic Characteristics of Marijuana Users and Non-Users

	In the past 30 days, did you use marijuana or hashish at least once?								
	Yes: n=439, 21.1% (95% CI 18.6, 23.6)			No: n=2,583, 78.9% (95% CI 76.4, 81.4)			Total: n=3,022		
	%	95% CI		%	95% CI		%	95% CI	
Home ownership***									
Own	44.2	37.6	50.9	63.6	60.7	66.6	59.5	56.8	62.3
Rent	46.6	39.7	53.6	30.7	27.9	33.5	34.1	31.4	36.8
Something else	9.1	4.4	13.8	5.7	3.9	7.4	6.4	4.7	8.1
Children in household									
No	71.4	64.8	78.0	68.4	65.5	71.2	69.0	66.4	71.7
Yes	28.6	22.0	35.2	31.6	28.8	34.5	31.0	28.3	33.6
Multiple	10.2	5.8	14.6	15.5	13.8	17.3	14.4	12.8	16.1
Region									
Boston	13.8	9.0	18.6	14.3	12.1	16.4	14.2	12.2	16.2
Central	13.3	9.1	17.5	14.6	12.7	16.4	14.3	12.6	16.0
Metrowest	18.3	12.6	24.0	22.1	19.8	24.5	21.3	19.1	23.6
Northeast	17.4	12.3	22.4	18.4	16.2	20.7	18.2	16.1	20.3
Southeast	18.8	12.9	24.6	18.9	16.7	21.1	18.9	16.8	21.0
Western	18.5	13.7	23.3	11.6	10.0	13.3	13.1	11.4	14.7

Note: *p<0.05; **p<0.01; ***p<0.001

Marijuana Attitudes and Perceptions

Table 3 presents attitudes and perceptions about marijuana. More than half of Massachusetts adults, 58.5%, favor the legalization of marijuana. As for risk perceptions, 20.0% of Massachusetts adults perceive marijuana to have no risks, 32.5% perceive it to have slight risks, 26.4% perceive moderate risks, and 21.0% perceive great risks.

We stratified data to examine attitudes and perceptions among Massachusetts adults who had used marijuana in the past 30 days compared with adults who had not. A majority of marijuana users, 96.5%, favor the legalization of marijuana, whereas less than half of non-users, 48.2%, favor marijuana legalization (p<0.001). A greater proportion of marijuana users than non-users perceive marijuana to have no health risks, or slight risks (p<0.001).

Table 3. Marijuana Attitudes and Perceptions of Marijuana Users and Non-Users

	In the past 30 days, did you use marijuana or hashish at least once?								
	Yes: n=439, 21.1% (95% CI 18.6, 23.6)			No: n=2,583, 78.9% (95% CI 76.4, 81.4)			Total: n=3,022		
	%	95% CI		%	95% CI		%	95% CI	
Favor marijuana legalization***									
No	3.5	1.1	5.9	51.8	48.9	54.6	41.5	38.9	44.1
Yes	96.5	94.1	98.9	48.2	45.4	51.1	58.5	55.9	61.1
Perceived marijuana risks***									
No risk	47.3	40.4	54.3	12.7	10.4	14.9	20.0	17.6	22.5
Slight risk	44.8	37.9	51.7	29.3	26.7	31.8	32.5	30.0	35.1
Moderate risk	4.7	2.7	6.7	32.3	29.7	34.8	26.4	24.2	28.6
Great risk	3.2	0.8	5.6	25.8	23.3	28.2	21.0	18.9	23.1

Note: *p<0.05; **p<0.01; ***p<0.001

Use of Alcohol and Other Substances

Table 4 presents past 30-day alcohol and other substance use among Massachusetts adults. Among all adults, 69.4% had consumed alcohol in the prior 30 days, and 4.1% had consumed another substance. Other substance use was defined as past 30-day use of any of the following substance types: non-prescribed opioids, cocaine/crack, heroin, non-medical anti-anxiety drugs, and other illicit substances. Prevalence rates were relatively small for each of the other substance categories, i.e., 0.9% for cocaine/crack, 0.1% for heroin, 1.3% for non-medical use of anti-anxiety substances, 1.4% for non-medical use of opioids, and 0.4% for other illegal substances.

We stratified data to examine alcohol and other substance use by adults who had used marijuana in the past 30 days compared with adults who had not. A greater proportion of marijuana users than non-users had used alcohol. Specifically, 82.1% of marijuana users had used alcohol, versus 66.0% of non-users (p<0.001). Also, a greater proportion of marijuana users than non-users had used other substances. Specifically, 9.8% of marijuana users had used other substances, versus 2.6% of non-users (p<0.01). Analysis of each substance type revealed that 3.8% of marijuana users had used non-prescribed opioids, versus 0.8% of non-users (p<0.05), and that similar proportions of adults in each group had past 30-day use of cocaine/crack, heroin, non-medical anti-anxiety drugs, and other illicit substances. Given the low rates of past 30-day use of each of these substances, interpretation of these results should be made with caution.

Table 4. Use of Alcohol and Other Substances of Marijuana Users and Non-Users

	In the past 30 days, did you use marijuana or hashish at least once?								
	Yes: n=439, 21.1% (95% CI 18.6, 23.6)			No: n=2,583, 78.9% (95% CI 76.4, 81.4)			Total: n=3,022		
	%	95% CI		%	95% CI		%	95% CI	
Substance use in past 30 days									
Alcohol***	82.1	76.8	87.4	66	63.2	68.8	69.4	66.9	71.9
Cocaine/crack	2.8	0.3	5.2	0.4	0.0	0.9	0.9	0.3	1.6
Heroin	.	.	.	0.1	0.0	0.2	0.1	0.0	0.2
Anti-anxiety, non-medical	1.3	0.0	2.8	1.3	0.4	2.1	1.3	0.5	2.0
Opioids, non-medical*	3.8	1.0	6.6	0.8	0.3	1.2	1.4	0.7	2.1
Other illegal substances	1.5	0.0	3.2	0.1	0.0	0.4	0.4	0.0	0.8
Other substances**	9.8	5.3	14.4	2.6	1.5	3.6	4.1	2.8	5.4

Note: *p<0.05; **p<0.01; ***p<0.001. Other substances” is defined as any past 30-day use of cocaine/crack, heroin, non-medical anti-anxiety substances, non-medical opioids, and other illegal substances.

Marijuana Consumption Patterns, Methods, and Expenditures

Table 5 presents marijuana consumption patterns, methods, and expenditures reported by Massachusetts adults who had used marijuana in the past 30 days. About half (50.6%) of marijuana users consumed it only by smoking, while 42.9% used more than one method of consumption. Fewer marijuana users vaporized or ate marijuana, 2.9% and 2.6%, respectively. Less than 1% only drank or dabbled marijuana, or only used it topically or sublingually.

More than half of Massachusetts adult marijuana users, 56.0%, report using marijuana only for adult non-medical purposes. Adults also use marijuana for medical reasons; 4% only used prescribed marijuana, 11.5% only used non-prescribed marijuana. In other words, 15.5% used either prescribed or not prescribed marijuana for medical reasons. More than one-quarter, 28.5%, reported both adult and medical marijuana use. Of Massachusetts adult marijuana users, 35.5% spent no money on marijuana in the past month, 31.5% spent between \$1 and \$80, and 33.0% spent \$81 or more.

Table 5. Marijuana Consumption Patterns, Methods, and Expenditures

	Adults who used marijuana in past 30 days (n=439)		
	%	95% CI	
How used marijuana, past 30 days			
Smoke	50.6	43.6	57.5
Vaporize	2.9	1.3	4.4
Eat	2.6	0.6	4.6
Drink	0.3	0.0	0.7
Topical	0.3	0.0	0.6
Sublingual	0.3	0.0	0.7
Dab	0.2	0.0	0.7
More than 1 route of administration	42.9	36.1	49.7
Reasons used marijuana in past 30 days			
Adult (non-medical) only	56.0	49.1	62.9
Medical (prescribed) only	4.0	1.8	6.2
Medical (not prescribed) only	11.5	7.3	15.6
Any medical (prescribed and not prescribed)	15.5	--	--
Both adult and any medical	28.5	22.3	34.8
Amount of money spent on marijuana in past 30 days			
\$0	35.5	28.9	42.1
\$1-80	31.5	24.8	38.3
\$81-800	33.0	26.2	39.7

Correlates of Marijuana Use

Table 6 presents results from the Poisson regression examining socio-demographics and other factors associated with past 30-day marijuana use (defined as a dichotomous variable, yes versus no) by Massachusetts adults. It is important to remember that because the survey used a cross-sectional design, the results shown here reflect factors that are associated with marijuana use and cannot be interpreted as being causally related to marijuana use. We report relative risk (RR) and 95% confidence intervals (CI). Men were more likely than women to use marijuana (RR=1.3; 95% CI: 1.1-1.6). Age is also associated with marijuana use. Compared to adults aged 18 to 20, adults aged 26 to 34 were less likely to use marijuana (RR=0.6; 95% CI: 0.4-0.9), as are those aged 35 to 64 (RR=0.3; 95% CI: 0.2-0.5), and adults aged 65 and older (RR=0.1; 95% CI: 0.1-0.2). Having a graduate degree, compared with having attained a High School education or less, was negatively associated with marijuana use (RR=0.5; 95% CI: 0.4-0.8). Renting a home, compared with owning a home, was positively associated with marijuana use (RR=1.5; 95% CI: 1.1-1.9). Having children in the home was negatively associated with marijuana use (RR=0.8; 95% CI: 0.6-1.0). Compared with living in Boston, living in the Northeast (RR=1.8; 95% CI: 1.2-2.7), Southeast (RR=1.8; 95% CI: 1.1-2.7), and Western (RR=2.0; 95% CI: 1.3, 3.0) regions of the state are each positively associated with marijuana use. Marijuana use is positively associated with

past 30-day use of alcohol (RR=1.9; 95% CI: 1.4-2.6) and other substances (RR=1.7; 95% CI: 1.3-2.4). See Table 6.

Table 6. Adjusted Relative Risk of Marijuana Use

	Adjusted Relative Risk	95% Confidence Interval	
Male (ref: Female)*	1.3	1.1	1.6
Age (ref: 18-20)			
21-25	0.8	0.5	1.3
26-34*	0.6	0.4	0.9
35-64***	0.3	0.2	0.5
65+***	0.1	0.1	0.2
Race/Ethnicity (ref: White, non-Hispanic)			
Hispanic	1.0	0.7	1.5
Black, non-Hispanic	1.1	0.7	1.7
Asian, non-Hispanic	0.6	0.2	1.2
Other, non-Hispanic	1.4	0.9	2.1
Education (ref: Less than high school)			
College	0.8	0.6	1.1
Graduate degree**	0.5	0.4	0.8
Home ownership (ref: own)			
Rent**	1.5	1.1	1.9
Something else	1.0	0.7	1.6
Children in household (ref: No)*	0.8	0.6	1.0
Region (ref: Boston)			
Metrowest	1.4	0.9	2.1
Northeast**	1.8	1.2	2.7
Southeast*	1.8	1.1	2.7
Central	1.5	0.9	2.3
Western**	2.0	1.3	3.0
Alcohol use, past 30 days (ref: No)***	1.9	1.4	2.6
Other substance use, past 30 days (ref: No)**	1.7	1.3	2.4

Note: *p<0.05; **p<0.01; ***p<0.001. Results are based on weighted, multivariable regression analysis.

Discussion

We found that 21.1% of adults in Massachusetts had used marijuana in the past 30 days. Estimates are substantially higher than those provided by other surveys. For example, as presented in Chapter 1, 5.2% of Massachusetts adults aged 26 or older reported recent use of marijuana in 2006, and 9.2% reported recent use in 2014. In the present study, 18.0% of adults aged 26 or older had used marijuana in the past 30 days. Increases in marijuana prevalence among Massachusetts adults may be attributable to shifts in public opinion regarding marijuana, and in marijuana-related law and public policy.

Men in Massachusetts are more likely than women to use marijuana, as are individuals aged 18 to 20. Marijuana prevalence rates are 25.9% for men and 17.0% for women, 54.4% for those aged 18 to 20 and 49.1% for those aged 21 to 25. Findings regarding the greater likelihood of marijuana use by men and younger adults remained significant in regression analysis which accounts for the effect of other factors on marijuana use. Relationships are more complex between marijuana use and other factors, in particular, race/ethnicity and education.

By race/ethnicity, prevalence of marijuana use is highest among Hispanics, at 27.1%, followed by 25.8% of Blacks, 20.1% of Whites, 10.4% of Asians, and 37.5% of other race/ethnic groups. Among marijuana users living in MA, most are White, 70.8%, and many fewer are Hispanic, 12.0%, Black, 7.1%, other, 6.9%, or Asian, 3.2%. In the regression analysis, which accounted for the effect of other factors, race/ethnicity was not associated with marijuana use, suggesting that the likelihood of using marijuana is similar for each group (compared to Whites), when other factors are accounted for. As for educational attainment, prevalence data and bivariate analysis indicate that a greater proportion of adults with a High School degree or college education use marijuana than adults with a graduate degree. In regression analysis, which accounts for the effect of other factors on marijuana use, adults with a college education are as likely to use marijuana as those with a high school education or less. In contrast, adults with a graduate degree are less likely to use marijuana than those with a High School education or less. Relationships between marijuana use, educational attainment, and other indicators of economic status are known to be complex and poorly understood. For example, college students face added risks for marijuana use that have been attributed to a diverse set of factors that include: overestimation among college students regarding how often the average student uses drugs (McCabe, 2008); perceptions among college students that drug use during their college years is normative (Cook, Bauermeister, Gordon-Messer & Zimmerman, 2013; Pischke et al., 2012); the expectation among college students that drugs will reduce social anxiety and facilitate the formation of new peer friendships (Buckner, 2013); and greater exposure to drug-using opportunities that exist on college campuses (Arria et al., 2008).

Patterns of marijuana use among college graduates have been attributed to age-graded changes in social roles and associated normative behavior that generally accompany the life transitions that this event signifies (Kandel & Chen, 2000). The present study

was not designed to explore these types of relationships, and therefore findings should be interpreted with caution.

By region, residents in the Western area of the state report the highest prevalence rate of past 30-day marijuana use, at 29.8%, with rates in other areas of the Commonwealth ranging from 20.9% to 18.2%. In Poisson regression analysis, compared with living in Boston, living in the Northeast, Southeast, and Western regions of the state are each positively associated with marijuana use. Findings suggest that the public health impacts of marijuana use may not be evenly distributed across the state. Other factors associated with a lower likelihood of marijuana use are home ownership and having children in home. Given the cross-sectional design of the study, we cannot determine the nature of these relationships and therefore these findings should not be interpreted as being causally related.

About 7 out of 10 Massachusetts adults consume alcohol, and 4 out of 100 consume another substance (e.g., non-prescribed opioids, cocaine/crack, heroin, non-medical anti-anxiety drugs, and other illicit substances). Notably, a greater proportion of Massachusetts marijuana users than non-users consume alcohol and other substances, particularly non-prescribed opioids, and use of alcohol and other substances is associated with a greater likelihood of using marijuana. The co-occurring use of marijuana with alcohol and other substances, particularly during adolescence and young adulthood, is well-established (Swift et al., 2012; Tzilos, Reddy, Caviness, Anderson & Stein, 2014).

Just over half of Massachusetts adults favored the legalization of marijuana, with double the proportion of marijuana users than non-users supporting legalization. As there have been dramatic shifts in public opinion regarding marijuana and in marijuana-related law and public policy (Pacula et al., 2005; Pacula, Kilmer, Wagenaar, Chaloupka, & Caulkins, 2014; Pew Research Center, 2014), the incidence and prevalence of both marijuana use and also marijuana use disorders are expected to increase (Budney & Moore, 2002; Hasin et al., 2017; Martins et al., 2016; Volkow, Baler, Compton, & Weiss, 2014). Of those who ever use marijuana, about 21% develop a marijuana use disorder (Caulkins, 2018). However, the proportion of marijuana users who meet disorder criteria is different by age. For example, national prevalence data indicate that in 2016, approximately 7.2 million young adults aged 18 to 25 were current users of marijuana, or 20.8% of young adults, and of these, 1.7 million had a marijuana use disorder in the past year, or 5.0% (SAMHSA, 2017). Expressed another way, these data indicate that about 24% of young adults aged 18 to 25 who use marijuana meet disorder criteria. Longitudinal studies have documented that while marijuana use can extend over many years of the life course, for most individual's problematic marijuana use is generally limited to young adulthood (Chen & Jacobsen, 2012; DeWit, Offord & Wong, 1997; Schulenberg et al., 2005), and only about 9% of marijuana users remain dependent on the substance over the long-term (Hall & Degenhardt, 2009). However, once a marijuana use disorder does develop, it is associated with increased risk of several diseases and poor health outcomes, including impaired respiratory function, cardiovascular disease, adverse effects on adolescent psychosocial development and

mental health, and residual cognitive impairment (Hall & Degenhardt, 2013). In the present study, we only examined marijuana use, and we did not include measurement of marijuana use disorders.

More than half of adult marijuana users in Massachusetts report using marijuana only for adult non-medical purposes, but a significant proportion also report using it for medical reasons. At the same time, a greater proportion of marijuana users than non-users perceive marijuana to have no health risks, or only slight risks, and marijuana users are less likely to perceive that marijuana poses moderate or great risks. Marijuana is primarily used for adult use because it induces euphoria, drowsiness, and feelings of relaxation (Inaba & Cohen, 2011). Individuals who use marijuana therapeutically report that it relieves conditions and symptoms such as glaucoma, nausea, AIDS-associated anorexia and wasting syndrome, chronic pain, inflammation, multiple sclerosis, and epilepsy (Volkow, Baler, Compton, & Weiss, 2014). When taken in combination with prescribed medications, however, marijuana may increase the risk of bleeding, change the impact of medications to address blood sugar levels and low blood pressure, interfere with the body's ability to process certain medications, and have other negative impacts. Studies are underway now to better understand the health risks and benefits of marijuana use.

Finally, Accountable Care Organizations and ongoing health care reforms are expected to bring more marijuana users into primary care and other health care settings (Tai et al., 2014; Gordon, Conley & Gordon, 2013). The National Institute on Drug Abuse and other organizations have published evidence-based guidelines on the screening, brief intervention, and treatment of marijuana and other substance use. Also, the proliferation of electronic health records (EHRs) provides the opportunity to track marijuana use, assess its potential interaction with other therapies, and treat it when needed (Fihn et al., 2014; Halamka, 2014; Longhurst, Harrington & Shah, 2014; Weil, 2014). However, given the special regulations that govern addiction healthcare records (e.g., 42 CFR) and reluctance among patients and physicians to report the illicit and stigmatized behaviors that marijuana use once entailed, clinicians may not document marijuana use or refrain from discussing its potential health impacts with patients.

Limitations and Strengths

Findings must be considered within the context of several limitations. The survey response rate was 21.7%. While typical of general population surveys like this one, if there was a response bias on a measure not accounted for by the weighting, generalizability may be limited. For example, findings may be impacted by response bias if adults who used marijuana were more likely to return the survey than adults who do not use marijuana. This could lead to overestimation of the prevalence of marijuana use. The cross-sectional survey design precludes determining the temporal sequencing of experiences and prevents drawing of causal inferences. For this reason, it is appropriate to interpret findings as highlighting those factors that are associated with, but not necessarily causally related to, the outcomes of interest.

Marijuana and other substance use were both self-reported, and not corroborated by testing of biological samples. Social desirability bias can lead to underestimates in survey research, however a unique contribution of this study is that it is the first to be conducted in Massachusetts after legalization of marijuana for adult use. Data was collected in late 2017, nearly one year after marijuana became legal for adult use by, and several years after legalization of medical marijuana in Massachusetts. Reporting of illegal behaviors (e.g. use of illicit drugs; driving under the influence of alcohol or drugs) may be underreported.

Small cell sizes for categories of some variables likely mean that models including them are underpowered. The survey omitted individuals aged 17 or younger and adults living in non-residential settings (e.g., incarcerated settings, group home residents, etc.). Therefore, findings may underrepresent certain groups that may be more likely to use marijuana. We did not explore associations comparing mental health conditions, adulthood trauma, or other known risk factors for marijuana use, whether associations are different among subgroups of adults (moderation), or the processes through which factors are associated with the outcomes of interest (mediation), constituting several areas for future research.

References

- Allen, J., & Holder, M. D. (2014). Marijuana use and well-being in university students. *Journal of Happiness Studies*, 15(2), 301–321. <https://doi.org/10.1007/s10902-013-9423-1>.
- Arria, A. M., Caldeira, K. M., O'Grady, K. E., Vincent, K. B., Fitzelle, D. B., Johnson, E. P., & Wish, E. D. (2008). Drug exposure opportunities and use patterns among college students: results of a longitudinal prospective cohort study. *Subst Abus*, 29(4), 19-38. doi: 10.1080/08897070802418451.
- Bachhuber MA, Saloner B, Cunningham CO, Barry CL. (2014) Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med*, Oct;174(10):1668-73.
- Buckner, J. D. (2013). College cannabis use: the unique roles of social norms, motives, and expectancies. *J Stud Alcohol Drugs*, 74(5), 720-726.
- Budney, A.J., Moore, B.A. (2002). Development and consequences of cannabis dependence. *Journal of Clinical Pharmacology*, 42(11 Supplement): 28S-33S.
- Cambron, C., Guttmannova, K., & Fleming, C. B. (2017). State and national contexts in evaluating cannabis laws: A case study of Washington State. *Journal of Drug Issues*, 47(1), 74–90. <https://doi.org/10.1177/0022042616678607>.
- Caulkins, J.P. (2018). The real dangers of marijuana. *National Affairs*, 35. Retrieved from <https://www.nationalaffairs.com/publications/detail/the-real-dangers-of-marijuana>.
- Chen, P., & Jacobson, K. C. (2012). Developmental trajectories of substance use from early adolescence to young adulthood: gender and racial/ethnic differences. *J Adolesc Health*, 50(2), 154-163. doi: 10.1016/j.jadohealth.2011.05.013.
- Cook, S. H., Bauermeister, J. A., Gordon-Messer, D., & Zimmerman, M. A. (2013). Online network influences on emerging adults' alcohol and drug use. *J Youth Adolesc*, 42(11), 1674-1686. doi: 10.1007/s10964-012-9869-1.
- DeWit, D. J., Offord, D. R., & Wong, M. (1997). Patterns of onset and cessation of drug use over the early part of the life course. *Health Educ Behav*, 24(6), 746-758.
- Fihn, S.D., Francis, J., Clancy, C., Nielson, C., Nelson, K., Rumsfeld, J., Cullen, T., Bates, J., Graham, G.L. (2014). Insights from advanced analytics at the Veterans Health Administration. *Health Affairs (Millwood)*, 33(7): 1203-1211.
- Gordon, A.J., Conley, J.W., Gordon, J.M. (2013). Medical consequences of marijuana use: a review of current literature. *Current Psychology Reports*, 15(12): 419.
- Halamka, J. (2007, November 12). Data, information, knowledge, and wisdom. [Web log post]. Retrieved from <http://geekdoctor.blogspot.com/2007/11/data-information-knowledge-and-wisdom.html>.
- Hall, W., Degenhardt, L. (2014). The adverse health effects of chronic cannabis use. *Drug Testing and Analysis*, 6(1-2): 39-45.
- Hall, W. & Degenhardt, L. (2009). Adverse health effects of non-medical cannabis use. *Lancet*, 374, 1383–1391.
- Hall, W. & Kozlowski, L.T. (2015). The diverging trajectories of cannabis and tobacco policies in the United States: reasons and possible implications. *Addiction*, 110(3), 241–242. <https://doi.org/10.1038/nbt.3121>.ChIP-nexus.
- Hasin DS, Sarvet AL, Cerdá M, Keyes KM, Stohl M, Galea S, Wall MM. (2017) US Adult

- Illicit Cannabis Use, Cannabis Use Disorder, and Medical Marijuana Laws: 1991-1992 to 2012-2013. *JAMA Psychiatry*, Jun 1;74(6):579-588.
- Inaba DS & Cohen WE. Uppers, downers, all arounders. Seventh Edition. CNS Productions, Inc. Medford OR.
- Kandel, D. B., & Chen, K. (2000). Types of marijuana users by longitudinal course. *J Stud Alcohol*, 61(3), 367-378.
- Keyes, K. M., Wall, M., Cerdá, M., Schulenberg, J., O'Malley, P. M., Galea, S., Hasin, D.S. (2016). How does state marijuana policy affect US youth? Medical marijuana laws, marijuana use and perceived harmfulness: 1991–2014. *Addiction*, 111(12), 2187–2195. <https://doi.org/10.1111/add.13523>.
- Longhurst, C.A., Harrington, R.A., Shah, N.H. (2014). A 'green button' for using aggregate patient data at the point of care. *Health Affairs (Millwood)*, 33(7): 1229-1235.
- Martins SS, Mauro CM, Santaella-Tenorio J, Kim JH, Cerda M, Keyes KM, Hasin DS, Galea S, Wall M. (2016). State-level medical marijuana laws, marijuana use and perceived availability of marijuana among the general U.S. population. *Drug Alcohol Depend*. Dec 1; 169:26-32.
- McCabe, S. E. (2008). Misperceptions of non-medical prescription drug use: a web survey of college students. *Addict Behav*, 33(5), 713-724. doi: 10.1016/j.addbeh.2007.12.008.
- Monte, A. A., Zane, R. D., & Heard, K. J. (2015). The implications of marijuana legalization in Colorado. *JAMA*, 313(3), 241–242. <https://doi.org/10.1038/nbt.3121.ChIP-nexus>.
- Olfson M, Wall MM, Liu SM, Blanco C. (2018). Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States. *Am J Psychiatry*. Jan 1;175(1):47-53.
- Pacula, R.L., Kilmer, B., Wagenaar, A.C., Chaloupka, F.J., Caulkins, J.P. (2014). Developing public health regulations for marijuana: lessons from alcohol and tobacco. *American Journal of Public Health*, 104(6): 1021-1028.
- Pacula, R.L., MacCoun, R., Reuter, P., Chriqui, J., Kilmer, B., Harris, K., Paoli, L., Schäfer, C. (2005). What does it mean to decriminalize marijuana? A cross-national empirical examination. *Advances in Health Economics and Health Services Research*, 16: 347-369.
- Pew Research Center. (2014). America's new drug policy landscape: Two-thirds favor treatment, not jail, for use of heroin, cocaine.
- Pischke, C. R., Zeeb, H., van Hal, G., Vriesacker, B., McAlaney, J., Bewick, B. M., . . . Mikolajczyk, R. T. (2012). A feasibility trial to examine the social norms approach for the prevention and reduction of licit and illicit drug use in European University and college students. *BMC Public Health*, 12, 882. doi: 10.1186/1471-2458-12-882.
- Powell D, Pacula RL, Jacobson M. (2018). Do medical marijuana laws reduce addictions and deaths related to pain killers? *J Health Econ*, Jan 30;58:29-42.
- Schulenberg JE, Merline AC, Johnston LD, O'Malley PM, Bachman JG, Laetz VB. (2005). Trajectories of Marijuana Use During the Transition to Adulthood: The Big Picture Based on National Panel Data. *J Drug Issues*, 35(2):255-279.
- Substance Abuse and Mental Health Services Administration. (2017). Key substance use and mental health indicators in the United States: Results from the 2016

- National Survey on Drug Use and Health (HHS Publication No. SMA 17-5044, NSDUH Series H-52). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from <https://www.samhsa.gov/data/>.
- Swift, A. (2013). For first time Americans favor legalizing marijuana. Retrieved from www.gallup.com.
- Swift, W., Coffey, C., Degenhardt, L., Carlin, J. B., Romaniuk, H., & Patton, G. C. (2012). Cannabis and progression to other substance use in young adults: findings from a 13-year prospective population-based study. *J Epidemiol Community Health, 66*(7), e26. doi: 10.1136/jech.2010.129056.
- Tai, B., Hu, L., Ghitza, U.E., Sparenborg, S., Van Veldhuisen, P., Lindblad, R. (2014). Patient registries for substance use disorders. *Substance Abuse and Rehabilitation, 5*: 81-86.
- Tzilos, G. K., Reddy, M. K., Caviness, C. M., Anderson, B. J., & Stein, M. D. (2014). Getting higher: co-occurring drug use among marijuana-using emerging adults. *J Addict Dis, 33*(3), 202-209. doi: 10.1080/10550887.2014.950024.
- Volkow, N.D., Baler, R.D., Compton, W.M., Weiss, S.R.B. (2014). Adverse Health Effects of Marijuana Use. *The New England Journal of Medicine, 370*: 2219-2227.
- Vyas MB, LeBaron VT, Gilson AM. (2018). The use of cannabis in response to the opioid crisis: A review of the literature. *Nurs Outlook, Jan - Feb;66*(1):56-65.
- Weil, A.R. (2014). Big data in health: a new era for research and patient care. *Health Affairs (Millwood), 33*(7): 1110.
- Zou, G. (2004). A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol, 159*(7), 702-706.

**Chapter 3: Use and Perceptions of Marijuana among Adult Medical
Use of Marijuana Patients in Massachusetts**

Introduction

This report provides data and analysis on the 2018 Medical Use of Marijuana Patient Survey, a component of the Massachusetts Department of Public Health 2018 Marijuana Baseline Study. The aim of this survey is to better understand the patterns of marijuana use, perceptions, and behaviors among medical use of marijuana patients in Massachusetts. Massachusetts Department of Public Health contracted with JSI Research & Training Institute in April 2018 to administer a survey among participants of the Massachusetts Medical Use of Marijuana Program. 42,796 participants of the Massachusetts Medical Use of Marijuana Program were invited through email to take the survey using a computer, smartphone, or tablet.

Methods

Data collection efforts were conducted in April 2018 by JSI Research & Training Institute in conjunction with Massachusetts Department of Public Health. All registered participants of the Massachusetts Medical Use of Marijuana Program were invited to complete the survey via an emailed link to Survey Gizmo. The survey incorporated 81 items covering topics such as demographics, marijuana and marijuana product use, methods of marijuana administration, perceptions of medical use of marijuana, driving and other issues related to marijuana use, alcohol consumption, non-medical use of prescription drugs and other substances, and combination substance use. Respondents were sent 2 reminder emails and given the option at the end of the survey to enter a lottery drawing of \$500, \$250, or \$100.

The analyses look both at individual item response summaries as well as investigating differences between gender (male vs. female), age (≤ 50 years old vs. > 50 years old), and education level ($<$ Bachelor's (4-year college) degree vs. \geq Bachelor's degree) through cross-tabulation comparisons. Chi-square tests for equality of proportions were run to detect significant differences in item response distribution across groups. Exact significance tests were used to test equality of proportions in cases where response categories were too small for reliable chi-square testing. In cases where mean statistics are presented, independent t-tests were run to detect significant differences between comparison groups. Highly statistically significant results are highlighted in the summary text throughout this report, and all tables present item response frequency, percentages, and results of statistical testing.

Appendix B contains all survey questions administered as well as guiding logic used to prompt or restrict respondents to relevant next questions based on their answers to previous items.

Results

Response Rate

Table 1 shows demographic characteristics of the overall survey sample compared to all eligible survey participants. All adult registered medical use of marijuana patients in the Massachusetts Medical Use of Marijuana Program were eligible for participation in the 2018 Medical Use of Marijuana Patient Survey (N=42,796). 6934 of these patients responded to the 2018 Medical Use of Marijuana Patient Survey, for a response rate of nearly 16%. There were no noticeable differences between 2018 survey respondent distributions and the full eligible population across gender, age, and county, suggesting that respondent population demographics are comparable to the overall eligible population of medical use of marijuana patients in Massachusetts.

Table 1. DPH Patient Survey Response Rate and Comparison of Sample Population

	Full Eligible Population (N=42,796)		2018 Survey Respondents (N=6934)	
Response Rate	15.93%			
Gender	N=42796	%	N=6818	%
Male	24349	(56.90)	3723	(54.61)
Female	18387	(42.96)	3056	(44.82)
Other / choose not to answer	60	(0.14)	39	(0.57)
Age (in years)	N=42796	%	N=6772	%
18 to 25	3471	(8.11)	477	(7.04)
26 to 35	8695	(20.32)	1256	(18.55)
36 to 50	11857	(27.71)	1851	(27.33)
51 to 64	12141	(28.37)	2100	(31.01)
65 or older	6632	(15.50)	1088	(16.07)
County	N=42796	%	N=6864	%
Barnstable	1567	(3.66)	245	(3.57)
Berkshire	1052	(2.46)	210	(3.06)
Bristol	3155	(7.37)	460	(6.70)
Dukes	95	(0.22)	23	(0.34)
Essex	4950	(11.57)	743	(10.82)
Franklin	670	(1.57)	156	(2.27)
Hampden	2974	(6.95)	501	(7.30)
Hampshire	1962	(4.58)	392	(5.71)
Middlesex	9969	(23.29)	1536	(22.38)
Nantucket	40	(0.09)	6	(0.09)
Norfolk	4808	(11.23)	639	(9.31)
Plymouth	3686	(8.61)	533	(7.77)
Suffolk	3936	(9.20)	658	(9.59)
Worcester	3876	(9.06)	606	(8.87)
Not provided	56	(0.13)	223	(0.02)

Respondent Demographics

Approximately equal proportions of all respondents were male compared to female (55% vs. 45%) or under 51 years old (53% vs. 47%). A majority of respondents were Non-Hispanic White (87%), followed by Hispanic (5%), and Non-Hispanic Black or African American (3%). Less than 3% of respondents identified as more than one race, or other (Asian, Native Hawaiian, Pacific Islander, American Indian, Alaska Native, or other). 98% of all respondents reported their highest level of education as at least high school graduation or GED, while over 50% reported receiving a Bachelor's degree or higher. Less than 10% reported an annual household income below \$15,000, with the majority reporting over \$40,000. Less than 1% of women were currently pregnant or breastfeeding.

Table 2A shows results of significance tests comparing demographic characteristics by gender. A significantly larger proportion of female than male respondents reported their highest education as a professional degree beyond a Bachelor's degree (27% vs. 22%). Female respondents reported annual household incomes between \$15,000 and \$75,000 compared to males (46% vs. 38%), while a larger proportion of male respondents than female reported annual household incomes above \$75,000 (53% vs. 44%).

Table 2B shows results of significance tests comparing demographic characteristics by age group. The racial distribution of respondents under the age of 51 was significantly more diverse than respondents over the age of 50, as exhibited by the proportion of non-Hispanic White respondents (83% vs. 93%). Most notably, a larger proportion of Hispanic respondents were under age 51 than over 50. A larger proportion of respondents over the age of 50 than under had professional degrees beyond a Bachelor's degree (29% vs. 20%). Older respondents reported annual household income earnings above \$100,000 at a higher rate than younger respondents (38% vs. 34%).

Table 2C shows results of significance tests comparing demographic characteristics by educational attainment. A larger proportion of respondents with at least a Bachelor's degree than respondents without a degree were aged 65 years or older (20% vs. 12%) or between 26 to 35 years old (20% vs. 17%), while a larger proportion of respondents without a Bachelor's degree were aged between 18 and 25 (10% vs. 4%) and 51 to 64 (33% vs. 29%). A larger proportion of respondents with at least a Bachelor's degree identified as non-Hispanic White compared to respondents with an educational attainment below a Bachelor's degree (90% vs. 84%). Respondents with at least a Bachelor's degree also reported annual household incomes above \$75,000 at higher rates than participants without a Bachelor's degree (63% vs. 33%).

Table 2A: DPH Patient Survey Characteristics of Respondents by Gender

	Total N %	Gender		p-value
		Male (N=3732)	Female (N=3056)	
Gender	6818			no test
Male	3723 54.61			
Female	3056 44.82			
Other / choose not to answer	39 0.57			
Age (in years)	6772			**
18 to 25	477 7.04	244 6.66	214 7.13	
26 to 35	1256 18.55	668 18.23	543 18.10	
36 to 50	1851 27.33	1012 27.62	819 27.30	
51 to 64	2100 31.01	1091 29.78	991 33.03	
65 or older	1088 16.07	649 17.71	433 14.43	
Race/Ethnicity	6672			ns
White or Caucasian, non-Hispanic	5834 87.44	3138 87.39	2623 87.70	
Black or African-American, non-Hispanic	188 2.82	102 2.84	83 2.77	
Asian, non-Hispanic	52 0.78	29 0.81	22 0.74	
Native Hawaiian, Pacific Islander, American Indian or Alaska Native, non- Hispanic	14 0.21	8 0.22	6 0.20	
More than one race, non-Hispanic	171 2.56	79 2.20	89 2.98	
Hispanic	323 4.84	183 5.10	133 4.45	
Other	90 1.35	52 1.45	35 1.17	

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

(Continued) Table 2A. DPH Patient Survey Characteristics of Respondents by Gender

	Total N %	Gender		p-value
		Male (N=3732)	Female (N=3056)	
Highest level of education completed	6877			****
Less than high school	131 1.90	91 2.45	37 1.21	
High school or GED	816 11.87	483 12.98	320 10.50	
Some college credit, less than Bachelor's degree	2335 33.95	1233 33.14	1066 34.96	
cBachelor's degree	1930 28.06	1097 29.48	804 26.37	
Professional degree beyond a Bachelor's degree	1665 24.21	817 21.96	822 26.96	
Annual household income (all sources)	6279			****
Less than \$15,000	578 9.21	285 8.39	275 9.85	
\$15,000 to \$39,999	1147 18.27	559 16.46	564 20.19	
\$40,000 to \$74,999	1475 23.49	743 21.88	713 25.53	
\$75,000 to \$99,999	847 13.49	467 13.75	369 13.21	
\$100,000 or more	2232 35.55	1342 39.52	872 31.22	
Currently Pregnant	3070			no test
No	3054 99.48			
Yes	16 0.52			
Currently Breastfeeding	3061			no test
No	3058 99.90			
Yes	3 0.10			

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

Table 2B: DPH Patient Survey Characteristics of Respondents by Age Group

	Total N %	Age Group		
		≤ 50 years (N=3584)	≥ 51 years (N=3188)	p-value
Gender	6818			****
Male	3723 54.61	1924 54.01	1740 54.79	
Female	3056 44.82	1576 44.24	1424 44.84	
Other / choose not to answer	39 0.57	37 1.04	2 0.06	
Age (in years)	6772			no test
18 to 25	477 7.04			
26 to 35	1256 18.55			
36 to 50	1851 27.33			
51 to 64	2100 31.01			
65 or older	1088 16.07			
Race/Ethnicity	6672			****
White or Caucasian, non-Hispanic	5834 87.44	2860 82.66	2868 92.52	
Black or African-American, non-Hispanic	188 2.82	124 3.58	64 2.06	
Asian, non-Hispanic	52 0.78	44 1.27	8 0.26	
Native Hawaiian, Pacific Islander,	14	5	9	
American Indian or Alaska Native, non-	0.21	0.14	0.29	
Hispanic				
More than one race, non-Hispanic	171 2.56	112 3.24	57 1.84	
Hispanic	323 4.84	265 7.66	55 1.77	
Other	90 1.35	50 1.45	39 1.26	

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

(Continued) Table 2B: DPH Patient Survey Characteristics of Respondents by Age Group

	Total N %	Age Group		
		≤ 50 years (N=3584)	≥ 51 years (N=3188)	p-value
Highest Level of Education Completed	6877			****
Less than high school	131 1.90	81 2.26	45 1.41	
High school or GED	816 11.87	434 12.13	367 11.53	
Some college credit, less than Bachelor's degree	2335 33.95	1235 34.53	1052 33.05	
Bachelor's degree	1930 28.06	1108 30.98	797 25.04	
Professional degree beyond a Bachelor's degree	1665 24.21	719 20.10	922 28.97	
Annual Household Income (all sources)	6279			****
Less than \$15,000	578 9.21	371 11.23	200 6.98	
\$15,000 to \$39,999	1147 18.27	619 18.73	504 17.58	
\$40,000 to \$74,999	1475 23.49	766 23.18	677 23.61	
\$75,000 to \$99,999	847 13.49	437 13.22	399 13.92	
\$100,000 or more	2232 35.55	1112 33.65	1087 37.91	
Currently Pregnant	3070			***
No	3054 99.48	1581 99.06	1417 99.93	
Yes	16 0.52	15 0.94	1 0.07	
Currently Breastfeeding	3061			ns
No	3058 99.90	1589 99.81	1413 100.00	
Yes	3 0.10	3 0.19	0 0.00	

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

Table 2C: DPH Patient Survey Characteristics of Respondents by Education

	Total N %	Education		
		< Bachelor's (N=3282)	≥ Bachelor's (N=3595)	p-value
Gender	6818			ns
Male	3723 54.61	1807 55.70	1914 53.70	
Female	3056 44.82	1423 43.87	1626 45.62	
Other / choose not to answer	39 0.57	14 0.43	24 0.67	
Age (in years)	6772			****
18 to 25	477 7.04	320 9.96	157 4.43	
26 to 35	1256 18.55	533 16.58	721 20.33	
36 to 50	1851 27.33	897 27.91	949 26.76	
51 to 64	2100 31.01	1076 33.48	1021 28.79	
65 or older	1088 16.07	388 12.07	698 19.68	
Race/Ethnicity	6672			****
White or Caucasian, non-Hispanic	5834 87.44	2693 84.39	3134 90.26	
Black or African-American, non-Hispanic	188 2.82	119 3.73	68 1.96	
Asian, non-Hispanic	52 0.78	17 0.53	35 1.01	
Native Hawaiian, Pacific Islander, American Indian or Alaska Native, non- Hispanic	14 0.21	13 0.41	1 0.03	
More than one race, non-Hispanic	171 2.56	91 2.85	80 2.30	
Hispanic	323 4.84	209 6.55	113 3.25	
Other	90 1.35	49 1.54	41 1.18	

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

(Continued) Table 2C: DPH Patient Survey Characteristics of Respondents by Education

	Total N %	Education		
		< Bachelor's (N=3282)	≥ Bachelor's (N=3595)	p-value
Highest level of education completed	6877			no test
Less than high school	131 1.90			
High school or GED	816 11.87			
Some college credit, less than Bachelor's degree	2335 33.95			
Bachelor's degree	1930 28.06			
Professional degree beyond a Bachelor's degree	1665 24.21			
Annual household income (all sources)	6279			****
Less than \$15,000	578 9.21	436 14.65	141 4.28	
\$15,000 to \$39,999	1147 18.27	777 26.11	368 11.18	
\$40,000 to \$74,999	1475 23.49	779 26.18	694 21.08	
\$75,000 to \$99,999	847 13.49	344 11.56	500 15.18	
\$100,000 or more	2232 35.55	640 21.51	1590 48.28	
Currently Pregnant	3070			ns
No	3054 99.48	1420 99.58	1626 99.39	
Yes	16 0.52	6 0.42	10 0.61	
Currently Breastfeeding	3061			ns
No	3058 99.90	1415 99.86	1636 99.94	
Yes	3 0.10	2 0.14	1 0.06	

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

Marijuana and Marijuana Product Use

Table 3A, 3B, and 3C show results of survey responses pertaining to marijuana and marijuana product use, with comparisons by gender, age group, and educational attainment, respectively. All survey respondents were asked to report on the number of days in the past 30 days that they used marijuana or marijuana products. On average, respondents reported marijuana use for 23.5 days out of 30. Over 60% of respondents reported marijuana use for over 20 out of 30 days, while approximately 8% reported no use. A slightly higher rate of respondents under the age of 51 reported at least 11 days of use compared to respondents over age 50 (82% vs. 76%). A larger proportion of respondents without a Bachelor's degree than respondents with a Bachelor's degree reported use for over 20 out of 30 days (65% vs. 56%).

Respondents who indicated having used marijuana or marijuana products at least once in the past 30 days were asked to report their total monthly expenditures on marijuana and marijuana products. Almost 40% of these respondents reported spending at least \$201 on marijuana or marijuana products in the past 30 days, while only 10% reported spending nothing. On average, male respondents reported spending approximately \$20 more than females, with a larger proportion of males than females spending at least \$151 (56% vs. 51%). Respondents under age 51 reported spending an average of \$82 more than older respondents, with a larger proportion of younger respondents than older spending at least \$151 (60% vs. 47%). Respondents without a Bachelor's degree spent approximately \$71 more than respondents with a Bachelor's degree, with a larger proportion of respondents without a Bachelor's spending at least \$151 (61% vs. 48%).

All survey respondents were asked to indicate the purpose of their marijuana use in the past 30 days. 93% of respondents reported medical use of marijuana certified by a medical practitioner, 6% reported medical use not certified by a medical practitioner, and 17% of respondents reported recreational use of marijuana. Respondents younger than 51 years old reported higher rates of recreational use than older respondents (20% vs. 14%). Respondents with a Bachelor's degree reported higher rates of recreational use than respondents without a Bachelor's degree (20% vs. 14%).

Table 3A: DPH Patient Survey Marijuana and Marijuana Products by Gender

	Total N %	Gender		
		Male (N=3732)	Female (N=3056)	p-value
Number of days in past 30 days using marijuana (Mean; Std.)	23.53 8.58	23.78 8.36	23.20 8.86	**
Number of days in past 30 days using marijuana	6640			*
0 days	529 7.97	278 7.78	237 8.01	
1-5 days	370 5.57	168 4.70	196 6.63	
6-10 days	495 7.45	260 7.28	230 7.78	
11-20 days	1223 18.42	662 18.54	546 18.46	
21-30 days	4023 60.59	2203 61.69	1748 59.11	
Money spent on marijuana in past 30 days (Mean; Std.) †	\$245.59 313.61	\$255.06 286.36	\$235.00 346.64	*
Total money spent on marijuana / products in past 30 days	4798			****
\$0	496 10.34	226 8.65	263 12.43	
\$1 - \$50	348 7.25	190 7.27	149 7.04	
\$51 to \$100	809 16.86	450 17.21	346 16.36	
\$101 to \$150	571 11.90	287 10.98	278 13.14	
\$151 to \$200	687 14.32	383 14.65	294 13.90	
\$201 or more	1887 39.33	1078 41.24	785 37.12	
Purpose of marijuana use ††				
Recreational (non-medical, e.g., to get high) only	1038 17.00	585 17.79	428 15.74	*
Medical use NOT certified by a qualified practitioner only	380 6.22	238 7.24	134 4.93	***
Medical use certified by a qualified practitioner only	5690 93.2	3029 92.09	2567 94.41	***
† Among respondents indicating use of marijuana or marijuana products at least once in past 30 days (N=6111) †† Percentages sum to more than 100% because respondents could choose more than one option *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 3B: DPH Patient Survey Marijuana and Marijuana Product Use by Age Group

	Total N %	Age Group		
		≤ 50 years (N=3584)	≥ 51 years (N=3188)	p-value
Number of Days in Past 30 Days Using Marijuana (Mean; Std.)	23.53 8.58	23.93 8.27	23.08 8.89	***
Number of days in past 30 days using marijuana	6640			****
0 days	529 7.97	243 7.01	268 8.76	
1-5 days	370 5.57	171 4.93	191 6.24	
6-10 days	495 7.45	221 6.37	266 8.69	
11-20 days	1223 18.42	664 19.15	546 17.84	
21-30 days	4023 60.59	2168 62.53	1790 58.48	
Money Spent on Marijuana in Past 30 Days (Mean; Std.) †	\$245.59 313.61	\$285.14 379.04	\$203.03 216.65	****
Total money spent on marijuana / products in past 30 days	4798			****
\$0	496 10.34	192 7.75	293 13.04	
\$1 - \$50	348 7.25	145 5.86	196 8.72	
\$51 to \$100	809 16.86	385 15.55	412 18.34	
\$101 to \$150	571 11.90	269 10.86	297 13.22	
\$151 to \$200	687 14.32	368 14.86	310 13.80	
\$201 or more	1887 39.33	1117 45.11	739 32.89	
Purpose of Marijuana Use †‡				
Recreational (non-medical, e.g., to get high) only	1038 17.00	651 20.20	381 13.66	****
Medical use NOT certified by a qualified practitioner only	380 6.22	172 5.34	203 7.28	*
Medical use certified by a qualified practitioner only	5690 93.2	3024 93.85	2578 92.40	**
† Among respondents indicating use of marijuana or marijuana products at least once in past 30 days (N=6111)				
‡ Percentages sum to more than 100% because respondents could choose more than one option				
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 3C: DPH Patient Survey Marijuana and Marijuana Products Use by Education

	Total N %	Education		
		< Bachelor's (N=3282)	≥ Bachelor's (N=3595)	p-value
Number of days in past 30 days using marijuana (Mean; Std.)	23.53 8.58	24.82 7.94	22.40 8.96	****
Number of days in past 30 days using marijuana	6640			****
0 days	529 7.97	286 9.06	242 6.98	
1-5 days	370 5.57	122 3.86	245 7.07	
6-10 days	495 7.45	180 5.70	314 9.06	
11-20 days	1223 18.42	507 16.06	713 20.58	
21-30 days	4023 60.59	2062 65.32	1951 56.31	
Money spent on marijuana in past 30 days (Mean; Std.) †	\$245.59 313.61	\$285.18 379.25	\$213.81 243.93	****
Total money spent on marijuana / products in past 30 days	4798			****
\$0	496 10.34	167 7.79	327 12.38	
\$1 - \$50	348 7.25	129 6.01	218 8.25	
\$51 to \$100	809 16.86	315 14.69	491 18.59	
\$101 to \$150	571 11.90	236 11.00	334 12.65	
\$151 to \$200	687 14.32	299 13.94	386 14.62	
\$201 or more	1887 39.33	999 46.57	885 33.51	
Purpose of marijuana use †‡				
Recreational (non-medical, e.g., to get high) only	1038 17.00	402 14.01	633 19.66	****
Medical use NOT certified by a qualified practitioner only	380 6.22	186 6.48	194 6.02	ns
Medical use certified by a qualified practitioner only	5690 93.2	2673 93.17	3000 93.17	ns
† Among respondents indicating use of marijuana or marijuana products at least once in past 30 days (N=6111)				
‡ Percentages sum to more than 100% because respondents could choose more than one option				
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Medical Conditions for Marijuana and Marijuana Product Use

Tables 4A, 4B, and 4C summarize results of survey responses pertaining to medical conditions for which marijuana and marijuana products were used, with comparisons by gender, age group, and educational attainment, respectively. Respondents who did not use marijuana or marijuana products for medical use in the past 30 days (whether certified or uncertified) were asked to indicate all medical conditions for which they used marijuana or marijuana products. Note that percentages in *Tables 4A, 4B, and 4C* add to more than 100% because of multiple conditions being treated at the same time.

The most common medical condition for which respondents indicated marijuana use was anxiety (60%), followed by chronic pain (46%), insomnia (43%), depression (42%), and stress (41%). Respondents also reported treating arthritis, headaches/migraines, muscle spasms, PTSD, and nausea at rates between 16 and 26%.

A significantly larger proportion of female respondents than male reported using marijuana or marijuana products to treat anxiety, arthritis, bowel distress, depression, fibromyalgia, headaches/migraines, multiple sclerosis, nausea, osteoarthritis, PTSD, vomiting, and “other”. A larger proportion of male respondents than female reported using marijuana or marijuana products to treat ADHD, alcohol dependency, diabetes, HIV/AIDS, and sleep apnea.

A larger proportion of respondents 51 years or older reported using marijuana or marijuana products to treat arthritis, cancer, chronic pain, diabetes, glaucoma, HIV/AIDS, hypertension, neuropathy, and osteoarthritis. A larger proportion of respondents under 51 years old reported using marijuana or marijuana products to treat ADHD, anxiety, bipolar disorder, bowel distress, depression, headaches/migraines, insomnia, loss of appetite, nausea, OCD, PTSD, stress, and vomiting.

Respondents with a Bachelor’s degree did not report using marijuana or marijuana products to treat any of the medical conditions at higher rates than respondents without a Bachelor’s degree. Respondents without a Bachelor’s degree reported using marijuana or marijuana products at higher rates than respondents with a Bachelor’s degree to treat ADHD, anxiety, arthritis, bipolar disorder, carpal tunnel, chronic pain, depression, diabetes, fibromyalgia, headaches/migraines, loss of appetite, muscle spasms, nausea, OCD, opioid use, PTSD, seizures, sleep apnea, and stress.

Table 4A: DPH Patient Survey Medical Use of Marijuana and Marijuana Product Use, Medical Conditions Treated by Gender

	Total N %	Gender		
		Male (N=3293)	Female (N=2720)	p-value
Marijuana used for medical purposes	6111			*
No	195 3.19	122 3.70	70 2.57	
Yes	5916 96.81	3171 96.30	2650 97.43	
Medical condition (s) for which respondent uses marijuana or marijuana products †‡	5916			
ADHD	711 12.02	424 13.37	260 9.81	****
Alcohol Dependency	164 2.77	120 3.78	42 1.58	****
Anxiety	3559 60.16	1773 55.91	1719 64.87	****
Arthritis	1563 26.42	784 24.72	759 28.64	***
Asthma	190 3.21	83 2.62	101 3.81	**
Bipolar Disorder	336 5.68	167 5.27	162 6.11	ns
Bowel Distress	562 9.50	232 7.32	318 12.00	****
Cancer	331 5.59	186 5.87	141 5.32	ns
Carpal Tunnel	214 3.62	101 3.19	111 4.19	*
Chronic Pain	2749 46.47	1456 45.92	1247 47.06	ns
Crohn's Disease	159 2.69	80 2.52	78 2.94	ns
Depression	2463 41.63	1213 38.25	1195 45.09	****
Diabetes	216 3.65	160 5.05	55 2.08	****
Fibromyalgia	444 7.51	76 2.40	359 13.55	****
Glaucoma	143 2.42	91 2.87	52 1.96	*

† Among respondents indicating medical use of marijuana or marijuana products (certified or uncertified)
‡ Percentages sum to more than 100% because respondents could choose more than one option
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

(Continued) Table 4A: DPH Patient Survey Medical Use of Marijuana and Marijuana Product Use, Medical Conditions Treated by Gender

	Total N %	Gender		
		Male (N=3293)	Female (N=2720)	p-value
Medical condition (s) for which respondent uses marijuana or marijuana products †‡	5916			
Headaches/Migraines	1185 20.03	464 14.63	693 26.15	****
Hepatitis C	56 0.95	41 1.29	14 0.53	**
HIV/AIDS	43 0.73	38 1.20	5 0.19	****
Huntington's Disease	2 0.03	1 0.03	1 0.04	ns
Hypertension	318 5.38	201 6.34	111 4.19	***
Insomnia	2524 42.66	1326 41.82	1152 43.47	ns
Loss of Appetite	744 12.58	396 12.49	323 12.19	ns
Multiple Sclerosis	140 2.37	45 1.42	94 3.55	****
Muscle Spasms	1050 17.75	516 16.27	518 19.55	**
Muscular Dystrophy	15 0.25	11 0.35	3 0.11	ns
Nausea	955 16.14	381 12.02	550 20.75	****
Neuropathy	611 10.33	287 9.05	313 11.81	***
OCD	276 4.67	119 3.75	152 5.74	***
Opioid Use	133 2.25	92 2.90	38 1.43	***
Osteoarthritis	466 7.88	183 5.77	280 10.57	****
PTSD	1005 16.99	464 14.63	512 19.32	****
Schizophrenia	17 0.29	13 0.41	2 0.08	*

† Among respondents indicating medical use of marijuana or marijuana products (certified or uncertified)
‡ Percentages sum to more than 100% because respondents could choose more than one option
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

(Continued)Table 4A: DPH Patient Survey Medical Use of Marijuana and Marijuana Product Use, Medical Conditions Treated by Gender

	Total N %	Gender		
		Male (N=3293)	Female (N=2720)	p-value
Medical condition (s) for which respondent uses marijuana or marijuana products †‡	5916			
Seizures	114 1.93	60 1.89	52 1.96	ns
Skin Conditions	149 2.52	60 1.89	84 3.17	**
Sleep Apnea	536 9.06	371 11.70	155 5.85	****
Stress	2408 40.70	1259 39.70	1095 41.32	ns
Tourette's Syndrome	18 0.30	16 0.50	2 0.08	**
Tremors	126 2.13	67 2.11	56 2.11	ns
Vomiting	224 3.79	88 2.78	129 4.87	****
Wasting	31 0.52	18 0.57	12 0.45	ns
Weight Loss	243 4.11	128 4.04	109 4.11	ns
Other	779 13.17	360 11.35	406 15.32	****

† Among respondents indicating medical use of marijuana or marijuana products (certified or uncertified)
‡ Percentages sum to more than 100% because respondents could choose more than one option
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

Table 4B: DPH Patient Survey Medical Use of Marijuana and Marijuana Product Use, Medical Conditions Treated by Age Group

	Total N %	Age Group		
		≤ 50 years (N=3224)	≥ 51 years (N=2793)	p-value
Marijuana used for medical purposes	6111			ns
No	195 3.19	114 3.54	78 2.79	
Yes	5916 96.81	3110 96.46	2715 97.21	
Medical condition (s) for which respondent uses marijuana or marijuana products †‡	5916			
ADHD	711 12.02	555 17.85	153 5.64	****
Alcohol Dependency	164 2.77	110 3.54	54 1.99	***
Anxiety	3559 60.16	2269 72.96	1243 45.78	****
Arthritis	1563 26.42	481 15.47	1053 38.78	****
Asthma	190 3.21	98 3.15	87 3.20	ns
Bipolar Disorder	336 5.68	268 8.62	64 2.36	****
Bowel Distress	562 9.50	347 11.16	207 7.62	****
Cancer	331 5.59	77 2.48	242 8.91	****
Carpal Tunnel	214 3.62	110 3.54	99 3.65	ns
Chronic Pain	2749 46.47	1293 41.58	1412 52.01	****
Crohn's Disease	159 2.69	96 3.09	58 2.14	*
Depression	2463 41.63	1611 51.80	823 30.31	****
Diabetes	216 3.65	68 2.19	144 5.30	****
Fibromyalgia	444 7.51	211 6.78	224 8.25	*
Glaucoma	143 2.42	31 1.00	111 4.09	****

† Among respondents indicating medical use of marijuana or marijuana products (certified or uncertified)
‡ Percentages sum to more than 100% because respondents could choose more than one option
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

(Continued) Table 4B: DPH Patient Survey Medical Use of Marijuana and Marijuana Product Use, Medical Conditions Treated by Age Group

	Total N %	Age Group		p-value
		≤ 50 years (N=3224)	≥ 51 years (N=2793)	
Medical condition (s) for which respondent uses marijuana or marijuana products †‡	5916			
Headaches/Migraines	1185 20.03	814 26.17	352 12.97	****
Hepatitis C	56 0.95	21 0.68	35 1.29	*
HIV/AIDS	43 0.73	13 0.42	30 1.10	**
Huntington's Disease	2 0.03	0 0.00	2 0.07	ns
Hypertension	318 5.38	112 3.60	200 7.37	****
Insomnia	2524 42.66	1434 46.11	1059 39.01	****
Loss of Appetite	744 12.58	529 17.01	203 7.48	****
Multiple Sclerosis	140 2.37	63 2.03	76 2.80	ns
Muscle Spasms	1050 17.75	542 17.43	494 18.20	ns
Muscular Dystrophy	15 0.25	9 0.29	6 0.22	ns
Nausea	955 16.14	638 20.51	298 10.98	****
Neuropathy	611 10.33	213 6.85	388 14.29	****
OCD	276 4.67	220 7.07	56 2.06	****
Opioid Use	133 2.25	76 2.44	55 2.03	ns
Osteoarthritis	466 7.88	95 3.05	359 13.22	****
PTSD	1005 16.99	634 20.39	352 12.97	****
Schizophrenia	17 0.29	14 0.45	3 0.11	*

† Among respondents indicating medical use of marijuana or marijuana products (certified or uncertified)
‡ Percentages sum to more than 100% because respondents could choose more than one option

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

(Continued) Table 4B: DPH Patient Survey Medical Use of Marijuana and Marijuana Product Use, Medical Conditions Treated by Age Group

	Total N %	Age Group		p-value
		≤ 50 years (N=3224)	≥ 51 years (N=2793)	
Medical condition (s) for which respondent uses marijuana or marijuana products †‡	5916			
Seizures	114 1.93	71 2.28	40 1.47	*
Skin Conditions	149 2.52	84 2.70	65 2.39	ns
Sleep Apnea	536 9.06	263 8.46	266 9.80	ns
Stress	2408 40.70	1529 49.16	845 31.12	****
Tourette's Syndrome	18 0.30	13 0.42	5 0.18	ns
Tremors	126 2.13	60 1.93	66 2.43	ns
Vomiting	224 3.79	164 5.27	55 2.03	****
Wasting	31 0.52	17 0.55	14 0.52	ns
Weight Loss	243 4.11	149 4.79	91 3.35	**
Other	779 13.17	374 12.03	401 14.77	**
† Among respondents indicating medical use of marijuana or marijuana products (certified or uncertified) ‡ Percentages sum to more than 100% because respondents could choose more than one option *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 4C: DPH Patient Survey Medical Use of Marijuana and Marijuana Product Use, Medical Conditions Treated by Education

	Total N %	Education		
		< Bachelor's (N=2871)	≥ Bachelor's (N=3223)	p-value
Marijuana used for medical purposes	6111			ns
No	195 3.19	86 3.00	109 3.38	
Yes	5916 96.81	2785 97.00	3114 96.62	
Medical condition (s) for which respondent uses marijuana or marijuana products †‡	5916			
ADHD	711 12.02	403 14.47	307 9.86	****
Alcohol Dependency	164 2.77	85 3.05	79 2.54	ns
Anxiety	3559 60.16	1784 64.06	1768 56.78	****
Arthritis	1563 26.42	835 29.98	725 23.28	****
Asthma	190 3.21	111 3.99	79 2.54	**
Bipolar Disorder	336 5.68	237 8.51	97 3.11	****
Bowel Distress	562 9.50	268 9.62	292 9.38	ns
Cancer	331 5.59	139 4.99	191 6.13	ns
Carpal Tunnel	214 3.62	138 4.96	76 2.44	****
Chronic Pain	2749 46.47	1460 52.42	1284 41.23	****
Crohn's Disease	159 2.69	64 2.30	95 3.05	ns
Depression	2463 41.63	1327 47.65	1128 36.22	****
Diabetes	216 3.65	131 4.70	84 2.70	****
Fibromyalgia	444 7.51	278 9.98	163 5.23	****
Glaucoma	143 2.42	68 2.44	75 2.41	ns

† Among respondents indicating medical use of marijuana or marijuana products (certified or uncertified)
‡ Percentages sum to more than 100% because respondents could choose more than one option
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

(Continued) Table 4C: DPH Patient Survey Medical Use of Marijuana and Marijuana Product Use, Medical Conditions Treated by Education

	Total N %	Education		p-value
		< Bachelor's (N=2871)	≥ Bachelor's (N=3223)	
Medical condition (s) for which respondent uses marijuana or marijuana products †‡	5916			
Headaches/Migraines	1185 20.03	669 24.02	510 16.38	****
Hepatitis C	56 0.95	37 1.33	18 0.58	**
HIV/AIDS	43 0.73	27 0.97	16 0.51	*
Huntington's Disease	2 0.03	1 0.04	1 0.03	ns
Hypertension	318 5.38	180 6.46	137 4.40	***
Insomnia	2524 42.66	1213 43.55	1304 41.88	ns
Loss of Appetite	744 12.58	438 15.73	302 9.70	****
Multiple Sclerosis	140 2.37	68 2.44	72 2.31	ns
Muscle Spasms	1050 17.75	617 22.15	428 13.74	****
Muscular Dystrophy	15 0.25	10 0.36	5 0.16	ns
Nausea	955 16.14	514 18.46	436 14.00	****
Neuropathy	611 10.33	325 11.67	282 9.06	**
OCD	276 4.67	165 5.92	111 3.56	****
Opioid Use	133 2.25	98 3.52	35 1.12	****
Osteoarthritis	466 7.88	221 7.94	244 7.84	ns
PTSD	1005 16.99	626 22.48	377 12.11	****
Schizophrenia	17 0.29	14 0.50	3 0.10	**

† Among respondents indicating medical use of marijuana or marijuana products (certified or uncertified)
‡ Percentages sum to more than 100% because respondents could choose more than one option
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

(Continued) Table 4C: DPH Patient Survey Medical Use of Marijuana and Marijuana Product Use, Medical Conditions Treated by Education

	Total N %	Education		p-value
		< Bachelor's (N=2871)	≥ Bachelor's (N=3223)	
Medical condition (s) for which respondent uses marijuana or marijuana products †‡	5916			
Seizures	114 1.93	74 2.66	38 1.22	****
Skin Conditions	149 2.52	73 2.62	76 2.44	ns
Sleep Apnea	536 9.06	315 11.31	221 7.10	****
Stress	2408 40.70	1266 45.46	1135 36.45	****
Tourette's Syndrome	18 0.30	10 0.36	8 0.26	ns
Tremors	126 2.13	71 2.55	54 1.73	*
Vomiting	224 3.79	127 4.56	95 3.05	**
Wasting	31 0.52	11 0.39	20 0.64	ns
Weight Loss	243 4.11	136 4.88	106 3.40	**
Other	779 13.17	347 12.46	430 13.81	ns

† Among respondents indicating medical use of marijuana or marijuana products (certified or uncertified)
‡ Percentages sum to more than 100% because respondents could choose more than one option
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

Methods of Marijuana / Marijuana Product Administration

Tables 5A, 5B, and 5C summarize results of survey responses pertaining to methods of marijuana and marijuana product administration used in the past 30 days, with comparisons by gender, age group, and educational attainment, respectively. Respondents were asked additional questions regarding their typical use of marijuana and the methods of marijuana or marijuana product administration used in the past 30 days. Further, for each method of administration reported, respondents were asked to provide further detail on the frequency and amount of marijuana product used. All respondents who indicated using marijuana at least once in the past 30 days were asked to indicate which methods of marijuana administration they used in the past 30 days. 16% of these respondents used only 1 method in the past 30 days, 26% used 2 methods, 26% used 3, and 31% used 4 or more. A larger proportion of respondents aged 51 or older than younger respondents reported using 1 or 2 methods (51% vs. 34%), while a larger proportion of younger respondents reported using 4 or 5+ methods (38% vs. 22%). A larger proportion of respondents without a Bachelor's degree than with a degree reported using 4 or more methods (34% vs. 27%), while a larger proportion of older respondents than younger reported using 2 or 3 methods (56% vs. 49%).

All respondents who indicated using marijuana or marijuana products at least once in the past 30 days were asked to report on the amount of THC and CBD in their typical marijuana or marijuana product use. 45% of these respondents reported typical use of marijuana or marijuana products that contain higher amounts of THC, 34% reported approximately equal amounts of THC and CBD, and 14% reported higher amounts of CBD. Almost 7% of respondents reported that they did not know. A larger proportion of males than females reported using products higher in THC (53% vs. 37%), while a larger proportion of females than males reported using products with higher amounts of CBD (17% vs. 11%) or equal amounts of THC and CBD (37% vs. 31%). A larger proportion of respondents under the age of 51 compared to older respondents reported using products higher in THC (50% vs. 40%), while a larger proportion of older respondents compared to younger reported using products higher in CBD (17% vs. 11%) or not knowing (9% vs. 5%). A slightly higher proportion of respondents without a Bachelor's degree than with a degree reported using products higher in THC or containing equal amounts of THC and CBD, while a slightly higher proportion of respondent with a Bachelor's degree reported using products higher in CBD.

Respondents who indicated using marijuana or marijuana products at least once in the past 30 days were asked about different methods of marijuana or marijuana product administration used in the past 30 days. Over 2 in 3 respondents reported smoking dried flower (65%) or using vaporized concentrate (62%). 51% reported consuming edible marijuana products. Approximately 1 in 4 respondents reported using vaporized dried flower (28%), applied topical cannabis oil, ointment, lotion, cream, salve, etc. to the skin (27%), and sublingual or orally administered uptake products (23%). 16% of respondents reported using dabbed marijuana products, 11% using oral capsules or tablets, and 5% drinking marijuana infused products.

A significantly larger proportion of male respondents than female reported using vaporized dried flower and dabbed marijuana products. A significantly larger proportion of female respondents than male reported using sublingual or orally administered uptake products and topical cannabis oil, ointment, lotion, cream, salve, etc. to the skin. A significantly larger proportion of respondents under age 51 than older respondents reported smoking dried flower, using vaporized dried flower, vaporized concentrate, dabbed marijuana products, edible marijuana products, and drinkable marijuana products. A significantly larger proportion of respondents without a Bachelor's degree than with a degree reported smoking dried flower and using dabbed marijuana products.

Table 5A: DPH Patient Survey Methods of Administration by Gender (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Gender		
		Male (N=3293)	Female (N=2720)	p-value
Number of administration methods used in the past 30 days				ns
0 methods	74 1.21	40 1.21	33 1.21	
1 method	953 15.59	555 16.85	387 14.23	
2 methods	1619 26.49	881 26.75	717 26.36	
3 methods	1598 26.15	833 25.30	744 27.35	
4 methods	1028 16.82	529 16.06	474 17.43	
5+ methods	839 13.73	455 13.82	365 13.42	
Typical marijuana / product use	6081			****
Higher in THC	2760 45.39	1722 52.50	999 36.96	
Higher in CBD	844 13.88	365 11.13	472 17.46	
Contain somewhat equal amounts of THC and CBD	2063 33.93	1010 30.79	1011 37.40	
Don't know / not sure	414 6.81	183 5.58	221 8.18	

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

**(Continues) Table 5A: DPH Patient Survey Methods of Administration by Gender
(Among 6,111 Respondents who Used Marijuana in Past 30 Days)**

Method of administration used (one time or more) in the past 30 days ‡	Total N %	Gender		
		Male (N=3293)	Female (N=2720)	p-value
Smoked dried flower	3921 65.12	2185 67.21	1667 62.39	***
Vaporized dried flower	1704 28.30	1033 31.77	642 24.03	****
Vaporized concentrated (cartridge/vape oil)	3751 62.30	2040 62.75	1647 61.64	ns
Dabbed marijuana products (butane hash oil, wax, shatter, etc.)	984 16.34	632 19.44	326 12.20	****
Ate marijuana products (brownies, cakes, cookies, etc.)	3074 51.05	1606 49.40	1410 52.77	**
Drank marijuana infused products (tea, cola, alcohol, etc.)	285 4.73	165 5.08	114 4.27	ns
Used sublingual (under the tongue) or orally administered uptake products (dissolvable strips, sublingual sprays, oil, tinctures, medicated lozenges, etc.)	1413 23.47	651 20.02	738 27.62	****
Used oral capsules/tablets	651 10.81	353 10.86	285 10.67	ns
Applied topical cannabis oil, ointment, lotion, cream, slave, etc. to skin	1600 26.57	638 19.62	933 34.92	****
Used rectal/vaginal cannabis suppositories	75 1.25	32 0.98	39 1.46	ns
Other	96 1.59	49 1.51	46 1.72	ns

‡ Percentages sum to more than 100% because respondents could choose more than one option
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

Table 5B: DPH Patient Survey Methods of Administration by Age Group (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Age Group		
		≤ 50 years (N=3224)	≥ 51 years (N=2793)	p-value
Number of administration methods used in the past 30 days				****
0 methods	74 1.21	34 1.05	37 1.32	
1 method	953 15.59	381 11.82	554 19.84	
2 methods	1619 26.49	724 22.46	858 30.72	
3 methods	1598 26.15	861 26.71	721 25.81	
4 methods	1028 16.82	632 19.60	381 13.64	
5+ methods	839 13.73	592 18.36	242 8.66	
Typical marijuana / product use	6081			****
Higher in THC	2760 45.39	1594 49.67	1123 40.42	
Higher in CBD	844 13.88	365 11.37	463 16.67	
Contain somewhat equal amounts of THC and CBD	2063 33.93	1100 34.28	935 33.66	
Don't know / not sure	414 6.81	150 4.67	257 9.25	

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

(Continued) Table 5B: DPH Patient Survey Methods of Administration by Age Group (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Age Group		
		≤ 50 years (N=3224)	≥ 51 years (N=2793)	p-value
Method of administration used (one time or more) in the past 30 days ‡				
Smoked dried flower	3921 65.12	2296 72.22	1573 57.24	****
Vaporized dried flower	1704 28.30	975 30.67	706 25.69	****
Vaporized concentrated (cartridge/vape oil)	3751 62.30	2174 68.39	1523 55.42	****
Dabbed marijuana products (butane hash oil, wax, shatter, etc.)	984 16.34	727 22.87	250 9.10	****
Ate marijuana products (brownies, cakes, cookies, etc.)	3074 51.05	1878 59.08	1166 42.43	****
Drank marijuana infused products (tea, cola, alcohol, etc.)	285 4.73	203 6.39	79 2.87	****
Used sublingual (under the tongue) or orally administered uptake products (dissolvable strips, sublingual sprays, oil, tinctures, medicated lozenges, etc.)	1413 23.47	692 21.77	708 25.76	***
Used oral capsules/tablets	651 10.81	357 11.23	285 10.37	ns
Applied topical cannabis oil, ointment, lotion, cream, slave, etc. to skin	1600 26.57	803 25.26	770 28.02	*
Used rectal/vaginal cannabis suppositories	75 1.25	48 1.51	26 0.95	ns
Other	96 1.59	45 1.42	49 1.78	ns
‡ Percentages sum to more than 100% because respondents could choose more than one option *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 5C: DPH Patient Survey Methods of Administration by Education (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Education		
		< Bachelor's (N=2871)	≥ Bachelor's (N=3223)	p-value
Number of administration methods used in the past 30 days				****
0 methods	74 1.21	44 1.53	30 0.93	
1 method	953 15.59	447 15.57	502 15.58	
2 methods	1619 26.49	721 25.11	892 27.68	
3 methods	1598 26.15	679 23.65	917 28.45	
4 methods	1028 16.82	521 18.15	503 15.61	
5+ methods	839 13.73	459 15.99	379 11.76	
Typical marijuana / product use	6081			**
Higher in THC	2760 45.39	1323 46.36	1433 44.64	
Higher in CBD	844 13.88	351 12.30	488 15.20	
Contain somewhat equal amounts of THC and CBD	2063 33.93	1005 35.21	1053 32.80	
Don't know / not sure	414 6.81	175 6.13	236 7.35	

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

Table 5C: DPH Patient Survey Methods of Administration by Education (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

Method of administration used (one time or more) in the past 30 days ‡	Total N %	Education		p-value
		< Bachelor's (N=2871)	≥ Bachelor's (N=3223)	
Smoked dried flower	3921 65.12	2052 72.36	1861 58.74	****
Vaporized dried flower	1704 28.30	742 26.16	956 30.18	***
Vaporized concentrated (cartridge/vape oil)	3751 62.30	1816 64.03	1925 60.76	**
Dabbed marijuana products (butane hash oil, wax, shatter, etc.)	984 16.34	595 20.98	389 12.28	****
Ate marijuana products (brownies, cakes, cookies, etc.)	3074 51.05	1452 51.20	1615 50.98	ns
Drank marijuana infused products (tea, cola, alcohol, etc.)	285 4.73	160 5.64	125 3.95	**
Used sublingual (under the tongue) or orally administered uptake products (dissolvable strips, sublingual sprays, oil, tinctures, medicated lozenges, etc.)	1413 23.47	613 21.61	796 25.13	**
Used oral capsules/tablets	651 10.81	277 9.77	373 11.77	*
Applied topical cannabis oil, ointment, lotion, cream, slave, etc. to skin	1600 26.57	761 26.83	835 26.36	ns
Used rectal/vaginal cannabis suppositories	75 1.25	34 1.20	41 1.29	ns
Other	96 1.59	50 1.76	46 1.45	ns

‡ Percentages sum to more than 100% because respondents could choose more than one option
 *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

Smoking Dried Flower

Tables 6A, 6B, and 6C summarize results of survey responses pertaining to smoking dried flower, with comparisons by gender, age group, and educational attainment, respectively. 65% of respondents who reported using marijuana or marijuana products in the past 30 days reported using smoked dried flower in a joint, bong, pipe, blunt, etc. the past 30 days. Smoking dried flower was significantly higher among respondents under age 51 compared to older respondents (72% vs. 57%) and respondents without a Bachelor's degree compared to respondents with at least a Bachelor's degree (72% vs. 59%).

Thirty-one percent of respondents who reported smoking dried flower in the past 30 days reported smoking dried flower multiple times per day, while 21% reported smoking dried flower less than once per week. A significantly larger proportion of respondents without a Bachelor's degree than with a degree reported smoking dried flower multiple times per day (37% vs. 24%), while a larger proportion of respondents with a Bachelor's

degree than without reported smoking dried flower less than once per week (25% vs. 17%) and more than once per week (but not as much as once per day) (34% vs. 27%).

Thirty-seven percent of respondents who reported smoking dried flower in the past 30 days reported using less than 1/8 oz. of dried flower in the past 30 days, 30% reported using between 1/8 and 1/2 oz., 22% reported using between 1/2 and 1 oz., and 6% reported using more than one oz. A larger proportion of male respondents than female reported using more than 1 oz. (8% vs. 4%), while a larger proportion of female respondents than male reported using no more than 1/8 oz. (42% vs. 33%) or an unknown amount (8% vs. 4%). A larger proportion of respondents less than 51 years old than older respondents reported using between 1/2 and 1 oz. (23% vs. 20%) and more than one oz. (7% vs. 5%), while a larger proportion of respondents older than 50 reported using up to 1/8 oz. (41% vs 34%) or between 1/8 and 1/4 oz. (15% vs. 13%). A larger proportion of respondents without a Bachelor's degree than with a degree reported using between 1/4 and 1/2 oz. (17% vs. 14%), 1/2 and 1 oz. (26% vs. 17%), and more than one oz. (8% vs. 4%). A larger proportion of respondents with a Bachelor's degree reported using up to 1/8 oz. (46% vs. 29%) and between 1/8 and 1/4 oz. (16% vs. 13%).

Table 6A: DPH Patient Survey Smoked Dried Flower by Gender (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Gender		p-value
		Male (N=3251)	Female (N=2672)	
Smoked dried flower in the past 30 days	6021			***
No	2100 34.88	1066 32.79	1005 37.61	
Yes	3921 65.12	2185 67.21	1667 62.39	
Frequency of smoking dried flower in a joint, bong, pipe, blunt, etc. †	3804			**
Less than once per week	802 21.08	404 19.13	386 23.75	
More than once per week (but not as much as once per day)	1142 30.02	645 30.54	475 29.23	
Once per day	693 18.22	390 18.47	295 18.15	
Multiple times per day	1167 30.68	673 31.87	469 28.86	
Total amount of dried flower smoked over past 30 days †	3827			****
0 to 1/8 ounce	1411 36.87	702 32.93	686 42.11	
1/8 to 1/4 ounce	537 14.03	316 14.82	212 13.01	
1/4 to 1/2 ounce	596 15.57	343 16.09	242 14.86	
1/2 to 1 ounce	835 21.82	521 24.44	303 18.60	
More than 1 ounce	228 5.96	162 7.60	62 3.81	
Don't know/not sure	220 5.75	88 4.13	124 7.61	
† Among respondents reporting smoking dried flower in past 30 days *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 6B: DPH Patient Survey Smoked Dried Flower by Age Group (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Age Group		
		≤ 50 years (N=3179)	≥ 51 years (N=2748)	p-value
Smoked dried flower in the past 30 days	6021			****
No	2100 34.88	883 27.78	1175 42.76	
Yes	3921 65.12	2296 72.22	1573 57.24	
Frequency of smoking dried flower in a joint, bong, pipe, blunt, etc. †	3804			*
Less than once per week	802 21.08	490 22.00	303 19.86	
More than once per week (but not as much as once per day)	1142 30.02	648 29.10	479 31.39	
Once per day	693 18.22	382 17.15	301 19.72	
Multiple times per day	1167 30.68	707 31.75	443 29.03	
Total amount of dried flower smoked over past 30 days †	3827			****
0 to 1/8 ounce	1411 36.87	766 34.15	631 41.11	
1/8 to 1/4 ounce	537 14.03	295 13.15	235 15.31	
1/4 to 1/2 ounce	596 15.57	362 16.14	223 14.53	
1/2 to 1 ounce	835 21.82	521 23.23	300 19.54	
More than 1 ounce	228 5.96	158 7.04	69 4.50	
Don't know/not sure	220 5.75	141 6.29	77 5.02	
† Among respondents reporting smoking dried flower in past 30 days *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 6C: DPH Patient Survey Smoked Dried Flower by Education (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Education		p-value
		< Bachelor's (N=2836)	≥ Bachelor's (N=3168)	
Smoked dried flower in the past 30 days	6021			****
No	2100 34.88	784 27.64	1307 41.26	
Yes	3921 65.12	2052 72.36	1861 58.74	
Frequency of smoking dried flower in a joint, bong, pipe, blunt, etc. †	3804			****
Less than once per week	802 21.08	339 17.14	461 25.36	
More than once per week (but not as much as once per day)	1142 30.02	526 26.59	613 33.72	
Once per day	693 18.22	383 19.36	310 17.05	
Multiple times per day	1167 30.68	730 36.91	434 23.87	
Total amount of dried flower smoked over past 30 days †	3827			****
0 to 1/8 ounce	1411 36.87	572 28.66	835 45.80	
1/8 to 1/4 ounce	537 14.03	250 12.53	285 15.63	
1/4 to 1/2 ounce	596 15.57	347 17.38	249 13.66	
1/2 to 1 ounce	835 21.82	528 26.45	307 16.84	
More than 1 ounce	228 5.96	163 8.17	65 3.57	
Don't know/not sure	220 5.75	136 6.81	82 4.50	

† Among respondents reporting smoking dried flower in past 30 days
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

Vaporized Marijuana Concentrate

Tables 8A, 8B, and 8C summarize results of survey responses pertaining to using vaporized marijuana concentrated, with comparisons by gender, age group, and educational attainment, respectively. 62% of respondents who reported using marijuana or marijuana products at least once in the past 30 days reported using vaporized marijuana concentrate in the past 30 days. Vaporized marijuana concentrate use was significantly higher among respondents under age 51 compared to older respondents (68% vs. 55%).

Thirty-six percent of respondents who reported using vaporized marijuana concentrate in the past 30 days reported using vaporized marijuana concentrate at least once per day, while 26% reported using vaporized marijuana concentrate less than once per week. A larger proportion of respondents without a Bachelor's degree than with a

degree reported using vaporized marijuana concentrate multiple times per day (25% vs. 19%) and once per day (16% vs. 13%), while a larger proportion of respondents with a Bachelor's degree than without reported using vaporized marijuana concentrate less than once per week (27% vs. 24%) and more than once per week (but not as much as once per day) (41% vs. 34%).

All respondents who reported using vaporized marijuana concentrate in the past 30 days were asked to indicate the amount of THC administered using vaporized marijuana concentrate over the past 30 days. The amount of THC reported by respondents should be interpreted with caution, as almost half of all respondents did not know how much THC they administered using vaporized marijuana concentrate. However, 40% of respondents reported administering between 1 and 150 mg of THC in the past 30 days using vaporized marijuana concentrate. A larger proportion of male respondents than female reported administering between 1 and 150 mg of THC (41% vs. 38%), while a larger proportion of female respondents than male reported that they did not know how much THC they administered using vaporized marijuana concentrate (51% vs. 42%). A larger proportion of respondents over the age of 50 than younger respondents reported that they did not know how much THC they administered using vaporized marijuana concentrate (50% vs. 43%).

All respondents who reported using vaporize marijuana concentrate in the past 30 days were asked to indicate the amount of CBD administered using vaporized marijuana concentrate over the past 30 days. The amount of CBD reported by respondents should be interpreted with caution, as more than 2 in 5 respondents did not know how much CBD they administered using vaporized marijuana concentrate. However, 38% of respondents reported administering between 1 and 150 mg of CBD in the past 30 days using vaporized marijuana concentrate. A larger proportion of male respondents than female reported administering between 1 and 150 mg of CBD (39% vs. 36%), while a larger proportion of female respondents than male reported that they did not know how much CBD they administered using vaporized marijuana concentrate (49% vs. 40%). A larger proportion of respondents over the age of 50 than younger respondents reported that they did not know how much CBD they administered using vaporized marijuana concentrate (48% vs. 41%), as did a larger proportion of respondents with a Bachelor's degree than without a degree (45% vs. 42%).

**Table 8A: DPH Patient Survey Vaporized Marijuana Concentrate by Gender
(Among 6,111 Respondents who Used Marijuana in Past 30 Days)**

	Total N %	Gender		
		Male (N=3251)	Female (N=2672)	p-value
Used vaporized marijuana concentrate in past 30 days	6021			ns
No	2270 37.70	1211 37.25	1025 38.36	
Yes	3751 62.30	2040 62.75	1647 61.64	
Frequency of using vaporized marijuana concentrate †	3551			ns
Less than once per week	909 25.60	500 25.75	397 25.61	
More than once per week (but not as much as once per day)	1346 37.90	770 39.65	556 35.87	
Once per day	505 14.22	261 13.44	234 15.10	
Multiple times per day	791 22.28	411 21.16	363 23.42	
Amount of THC administered † ‡	3661			****
0 mg past 30 days	58 1.58	21 1.06	37 2.30	
Between 1 and 150 mg in past 30 days	1447 39.52	818 41.15	607 37.66	
Between 151 and 300 mg in past 30 days	288 7.87	194 9.76	90 5.58	
More than 300 mg in past 30 days	182 4.97	123 6.19	53 3.29	
Don't know/not sure	1686 46.05	832 41.85	825 51.18	
Amount of CBD administered † ‡	3635			****
0 mg past 30 days	428 11.77	265 13.47	159 9.89	
Between 1 and 150 mg in past 30 days	1368 37.63	764 38.82	581 36.15	
Between 151 and 300 mg in past 30 days	198 5.45	116 5.89	76 4.73	
More than 300 mg in past 30 days	39 1.07	28 1.42	11 0.68	
Don't know/not sure	1602 44.07	795 40.40	780 48.54	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 8B: 2018 Marijuana Survey Results - Vaporized Marijuana Concentrate by Age Group (Among 6111 respondents indicating marijuana use in past 30 days)

	Total N %	Age Group		
		≤ 50 years (N=3179)	≥ 51 years (N=2748)	p-value
Used vaporized marijuana concentrate in past 30 days	6021			****
No	2270 37.70	1005 31.61	1225 44.58	
Yes	3751 62.30	2174 68.39	1523 55.42	
Frequency of using vaporized marijuana concentrate †	3551			*
Less than once per week	909 25.60	543 26.36	351 24.32	
More than once per week (but not as much as once per day)	1346 37.90	770 37.38	559 38.74	
Once per day	505 14.22	269 13.06	230 15.94	
Multiple times per day	791 22.28	478 23.20	303 21.00	
Amount of THC administered † ‡	3661			****
0 mg past 30 days	58 1.58	27 1.27	30 2.02	
Between 1 and 150 mg in past 30 days	1447 39.52	839 39.56	588 39.54	
Between 151 and 300 mg in past 30 days	288 7.87	198 9.34	88 5.92	
More than 300 mg in past 30 days	182 4.97	143 6.74	36 2.42	
Don't know/not sure	1686 46.05	914 43.09	745 50.10	
Amount of CBD administered † ‡	3635			****
0 mg past 30 days	428 11.77	258 12.22	160 10.88	
Between 1 and 150 mg in past 30 days	1368 37.63	814 38.56	536 36.44	
Between 151 and 300 mg in past 30 days	198 5.45	137 6.49	59 4.01	
More than 300 mg in past 30 days	39 1.07	32 1.52	7 0.48	
Don't know/not sure	1602 44.07	870 41.21	709 48.20	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 8C: 2018 Marijuana Survey Results - Vaporized Marijuana Concentrate by Education (Among 6111 respondents indicating marijuana use in past 30 days)

	Total N %	Education		
		< Bachelor's (N=2836)	≥ Bachelor's (N=3168)	p-value
Used vaporized marijuana concentrate in past 30 days	6021			**
No	2270 37.70	1020 35.97	1243 39.24	
Yes	3751 62.30	1816 64.03	1925 60.76	
Frequency of using vaporized marijuana concentrate †	3551			****
Less than once per week	909 25.60	412 24.36	495 26.73	
More than once per week (but not as much as once per day)	1346 37.90	582 34.42	763 41.20	
Once per day	505 14.22	266 15.73	238 12.85	
Multiple times per day	791 22.28	431 25.49	356 19.22	
Amount of THC administered † ‡	3661			***
0 mg past 30 days	58 1.58	21 1.19	37 1.96	
Between 1 and 150 mg in past 30 days	1447 39.52	689 39.04	756 40.06	
Between 151 and 300 mg in past 30 days	288 7.87	152 8.61	136 7.21	
More than 300 mg in past 30 days	182 4.97	109 6.18	73 3.87	
Don't know/not sure	1686 46.05	794 44.99	885 46.90	
Amount of CBD administered † ‡	3635			****
0 mg past 30 days	428 11.77	204 11.63	224 11.97	
Between 1 and 150 mg in past 30 days	1368 37.63	655 37.34	711 37.98	
Between 151 and 300 mg in past 30 days	198 5.45	123 7.01	75 4.01	
More than 300 mg in past 30 days	39 1.07	28 1.60	11 0.59	
Don't know/not sure	1602 44.07	744 42.42	851 45.46	

† Among respondents reporting using vaporized marijuana concentrate in the past 30 days

‡ Total monthly amount consumed

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

Dabbed Marijuana Products

Tables 9A, 9B, and 9C summarize results of survey responses pertaining to dabbing marijuana products, with comparisons by gender, age group, and educational attainment, respectively. 16% of respondents who indicated using marijuana or marijuana products at least once in the past 30 days reported using dabbed marijuana

products in the past 30 days. Dabbing was significantly higher among male respondents compared to female (19% vs. 12%), respondents under age 51 compared to older respondents (23% vs. 9%), and respondents without a Bachelor's degree compared to respondents with a degree (21% vs. 12%).

Twenty-eighty percent of respondents who reported dabbing marijuana products in the past 30 days reported dabbing marijuana products at least once per day, while 45% reported dabbing less than once per week. There were no significant differences in reported dabbing by gender, age, or education.

All respondents who reported dabbing marijuana products in the past 30 days were asked to indicate the amount of THC administered by dabbing marijuana products over the past 30 days. The amount of THC reported by respondents should be interpreted with caution, as more than 2 in 5 respondents did not know how much THC they administered through dabbing marijuana products. However, 39% of respondents reported administering between 1 and 150 mg of THC in the past 30 days by dabbing marijuana products. A larger proportion of respondents over the age of 50 than younger respondents reported that they did not know how much THC they administered using vaporized marijuana concentrate (47% vs. 41%).

All respondents who reported dabbing marijuana products in the past 30 days were asked to indicate the amount of CBD administered by dabbing marijuana products over the past 30 days. The amount of CBD reported by respondents should be interpreted with caution, as approximately 2 in 5 respondents did not know how much CBD they administered through dabbing marijuana products. However, 35% of respondents reported administering between 1 and 150 mg of CBD in the past 30 days by dabbing.

Table 9A: DPH Patient Survey Dabbing Marijuana Products by Gender (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Gender		
		Male (N=3251)	Female (N=2672)	p-value
Dabbed marijuana products in the past 30 days	6021			****
No	5037 83.66	2619 80.56	2346 87.80	
Yes	984 16.34	632 19.44	326 12.20	
Frequency of dabbing marijuana †	911			ns
Less than once per week	408 44.79	259 44.43	139 45.57	
More than once per week (but not as much as once per day)	247 27.11	156 26.76	86 28.20	
Once per day	84 9.22	58 9.95	23 7.54	
Multiple times per day	172 18.88	110 18.87	57 18.69	
Amount of THC administered † ‡	952			**
0 mg past 30 days	17 1.79	11 1.80	6 1.89	
Between 1 and 150 mg in past 30 days	374 39.29	230 37.70	133 41.82	
Between 151 and 300 mg in past 30 days	105 11.03	80 13.11	22 6.92	
More than 300 mg in past 30 days	51 5.36	40 6.56	10 3.14	
Don't know/not sure	405 42.54	249 40.82	147 46.23	
Amount of CBD administered † ‡	951			ns
0 mg past 30 days	165 17.35	107 17.60	54 16.93	
Between 1 and 150 mg in past 30 days	334 35.12	214 35.20	113 35.42	
Between 151 and 300 mg in past 30 days	56 5.89	40 6.58	15 4.70	
More than 300 mg in past 30 days	7 0.74	3 0.49	4 1.25	
Don't know/not sure	389 40.90	244 40.13	133 41.69	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 9B: DPH Patient Survey Dabbing Marijuana Products by Age Group (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Age Group		
		≤ 50 years (N=3179)	≥ 51 years (N=2748)	p-value
Dabbed marijuana products in the past 30 days	6021			****
No	5037 83.66	2452 77.13	2498 90.90	
Yes	984 16.34	727 22.87	250 9.10	
Frequency of dabbing marijuana †	911			ns
Less than once per week	408 44.79	299 43.78	107 48.20	
More than once per week (but not as much as once per day)	247 27.11	181 26.50	63 28.38	
Once per day	84 9.22	67 9.81	17 7.66	
Multiple times per day	172 18.88	136 19.91	35 15.77	
Amount of THC administered † ‡	952			****
0 mg past 30 days	17 1.79	7 0.99	10 4.15	
Between 1 and 150 mg in past 30 days	374 39.29	273 38.78	101 41.91	
Between 151 and 300 mg in past 30 days	105 11.03	93 13.21	10 4.15	
More than 300 mg in past 30 days	51 5.36	44 6.25	6 2.49	
Don't know/not sure	405 42.54	287 40.77	114 47.30	
Amount of CBD administered † ‡	951			*
0 mg past 30 days	165 17.35	122 17.38	41 16.94	
Between 1 and 150 mg in past 30 days	334 35.12	244 34.76	87 35.95	
Between 151 and 300 mg in past 30 days	56 5.89	51 7.26	5 2.07	
More than 300 mg in past 30 days	7 0.74	7 1.00	0 0.00	
Don't know/not sure	389 40.90	278 39.60	109 45.04	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 9C: DPH Patient Survey Dabbing Marijuana Products by Education (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

Table 9C: 2018 Marijuana Survey Results - DABBING MARIJUANA PRODUCTS by EDUCATION (Among 6111 respondents indicating marijuana use in past 30 days)				
	Total N %	Education		
		< Bachelor's (N=2836)	≥ Bachelor's (N=3168)	p-value
Dabbed marijuana products in the past 30 days	6021			****
No	5037 83.66	2241 79.02	2779 87.72	
Yes	984 16.34	595 20.98	389 12.28	
Frequency of dabbing marijuana †	911			ns
Less than once per week	408 44.79	237 43.25	171 47.11	
More than once per week (but not as much as once per day)	247 27.11	145 26.46	102 28.10	
Once per day	84 9.22	51 9.31	33 9.09	
Multiple times per day	172 18.88	115 20.99	57 15.70	
Amount of THC administered † ‡	952			ns
0 mg past 30 days	17 1.79	10 1.74	7 1.85	
Between 1 and 150 mg in past 30 days	374 39.29	229 39.90	145 38.36	
Between 151 and 300 mg in past 30 days	105 11.03	68 11.85	37 9.79	
More than 300 mg in past 30 days	51 5.36	32 5.57	19 5.03	
Don't know/not sure	405 42.54	235 40.94	170 44.97	
Amount of CBD administered † ‡	951			ns
0 mg past 30 days	165 17.35	91 15.88	74 19.58	
Between 1 and 150 mg in past 30 days	334 35.12	210 36.65	124 32.80	
Between 151 and 300 mg in past 30 days	56 5.89	41 7.16	15 3.97	
More than 300 mg in past 30 days	7 0.74	5 0.87	2 0.53	
Don't know/not sure	389 40.90	226 39.44	163 43.12	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Edible Marijuana Products

Tables 10A, 10B, and 10C summarize results of survey responses pertaining to consuming edible marijuana products, with comparisons by gender, age group, and educational attainment, respectively. 51% of respondents who reported using marijuana

at least once in the past 30 days reported using edible marijuana products in the past 30 days. A larger proportion of female respondents than male (53% vs. 49%) and respondents under age 50 than older (59% vs. 42%) reported edible marijuana use.

Twelve percent of respondents who reported using edible marijuana products in the past 30 days reported using these products at least once per day, while 61% reported using these products less than once per week. A larger proportion of respondents less than 51 years old than older respondents reported using edible marijuana products less than once per week (66% vs. 52%), while a larger proportion of older respondents than younger reported these products more than once per week (31% vs. 25%) and once per day (14% vs. 7%).

All respondents who used edible marijuana products in the past 30 days were asked to indicate the amount of THC administered by using these products over the past 30 days. The amount of THC reported by respondents should be interpreted with caution, as almost 1 in 4 respondents did not know how much THC they administered. However, 59% of respondents reported administering between 1 and 150 mg of THC in the past 30 days by through edible marijuana products. A larger proportion of male respondents than female reported administering between 150 and 300 mg of THC (13% vs. 8%), while a larger proportion of female respondents than male reported that they did not know (27% vs. 22%). A larger proportion of respondents under the age of 51 than older respondents reported administering between 150 and 300 mg of THC (12% vs. 9%), while a larger proportion of older respondents than younger reported that they did not know how much THC they administered through edible marijuana products (27% vs. 23%). A larger proportion of respondents with a Bachelor's degree than respondents without a degree reported administering between 1 and 150 mg of THC through edible marijuana products (63% vs. 54%), while a larger proportion of respondents without a Bachelor's degree reported that they did not know (28% vs. 22%).

All respondents who used edible marijuana products in the past 30 days were asked to indicate the amount of CBD administered by using edible marijuana products over the past 30 days. The amount of CBD reported by respondents should be interpreted with caution, as approximately 1 in 3 respondents did not know how much CBD they administered through edible marijuana products. However, 45% of respondents reported administering between 1 and 150 mg of CBD in the past 30 days through edible marijuana products.

Table 10A: DPH Patient Survey Edible Marijuana Products by Gender (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Gender		
		Male (N=3251)	Female (N=2672)	p-value
Used edible marijuana or marijuana products in the past 30 days	6021			**
No	2947 48.95	1645 50.60	1262 47.23	
Yes	3074 51.05	1606 49.40	1410 52.77	
Frequency of using edible marijuana or marijuana products †	2941			*
Less than once per week	1781 60.56	937 61.24	806 59.48	
More than once per week (but not as much as once per day)	798 27.13	431 28.17	357 26.35	
Once per day	284 9.66	128 8.37	151 11.14	
Multiple times per day	78 2.65	34 2.22	41 3.03	
Amount of THC administered † ‡	3000			****
0 mg past 30 days	80 2.67	36 2.30	44 3.19	
Between 1 and 150 mg in past 30 days	1770 59.00	918 58.70	817 59.20	
Between 151 and 300 mg in past 30 days	332 11.07	211 13.49	112 8.12	
More than 300 mg in past 30 days	82 2.73	52 3.32	28 2.03	
Don't know/not sure	736 24.53	347 22.19	379 27.46	
Amount of CBD administered † ‡	2981			***
0 mg past 30 days	488 16.37	284 18.36	194 14.08	
Between 1 and 150 mg in past 30 days	1332 44.68	688 44.47	619 44.92	
Between 151 and 300 mg in past 30 days	134 4.50	77 4.98	53 3.85	
More than 300 mg in past 30 days	28 0.94	20 1.29	8 0.58	
Don't know/not sure	999 33.51	478 30.90	504 36.57	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 10B: DPH Patient Survey Edible Marijuana Products by Age Group (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Age Group		
		≤ 50 years (N=3179)	≥ 51 years (N=2748)	p-value
Used edible marijuana or marijuana products in the past 30 days	6021			****
No	2947 48.95	1301 40.92	1582 57.57	
Yes	3074 51.05	1878 59.08	1166 42.43	
Frequency of using edible marijuana or marijuana products †	2941			****
Less than once per week	1781 60.56	1181 65.76	584 52.19	
More than once per week (but not as much as once per day)	798 27.13	450 25.06	343 30.65	
Once per day	284 9.66	121 6.74	159 14.21	
Multiple times per day	78 2.65	44 2.45	33 2.95	
Amount of THC administered † ‡	3000			****
0 mg past 30 days	80 2.67	39 2.13	39 3.41	
Between 1 and 150 mg in past 30 days	1770 59.00	1083 59.28	672 58.74	
Between 151 and 300 mg in past 30 days	332 11.07	222 12.15	106 9.27	
More than 300 mg in past 30 days	82 2.73	65 3.56	17 1.49	
Don't know/not sure	736 24.53	418 22.88	310 27.10	
Amount of CBD administered † ‡	2981			***
0 mg past 30 days	488 16.37	325 17.86	156 13.78	
Between 1 and 150 mg in past 30 days	1332 44.68	805 44.23	514 45.41	
Between 151 and 300 mg in past 30 days	134 4.50	94 5.16	39 3.45	
More than 300 mg in past 30 days	28 0.94	21 1.15	7 0.62	
Don't know/not sure	999 33.51	575 31.59	416 36.75	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 10C: DPH Patient Survey Edible Marijuana Products by Education (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

Table 10C: 2018 Marijuana Survey Results - EDIBLE MARIJUANA PRODUCTS by EDUCATION (Among 6111 respondents indicating marijuana use in past 30 days)				
	Total N %	Education		
		< Bachelor's (N=2836)	≥ Bachelor's (N=3168)	p-value
Used edible marijuana or marijuana products in the past 30 days	6021			ns
No	2947 48.95	1384 48.80	1553 49.02	
Yes	3074 51.05	1452 51.20	1615 50.98	
Frequency of using edible marijuana or marijuana products †	2941			**
Less than once per week	1781 60.56	845 61.19	930 59.88	
More than once per week (but not as much as once per day)	798 27.13	357 25.85	441 28.40	
Once per day	284 9.66	129 9.34	155 9.98	
Multiple times per day	78 2.65	50 3.62	27 1.74	
Amount of THC administered † ‡	3000			****
0 mg past 30 days	80 2.67	43 3.04	37 2.35	
Between 1 and 150 mg in past 30 days	1770 59.00	767 54.17	1001 63.47	
Between 151 and 300 mg in past 30 days	332 11.07	171 12.08	161 10.21	
More than 300 mg in past 30 days	82 2.73	45 3.18	37 2.35	
Don't know/not sure	736 24.53	390 27.54	341 21.62	
Amount of CBD administered † ‡	2981			*
0 mg past 30 days	488 16.37	210 14.91	277 17.69	
Between 1 and 150 mg in past 30 days	1332 44.68	629 44.67	701 44.76	
Between 151 and 300 mg in past 30 days	134 4.50	74 5.26	60 3.83	
More than 300 mg in past 30 days	28 0.94	18 1.28	10 0.64	
Don't know/not sure	999 33.51	477 33.88	518 33.08	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Drinkable Marijuana Products

Tables 11A, 11B, and 11C summarize results of survey responses pertaining to consuming drinkable marijuana products, with comparisons by gender, age group, and educational attainment, respectively. 5% of respondents who reported using marijuana or marijuana products at least once in the past 30 days reported using drinkable marijuana products in the past 30 days. Consuming drinkable marijuana products was significantly higher among respondents under age 51 compared to older respondents (6% vs. 3%) and respondents without a Bachelor's degree compared to respondents with a degree (6% vs. 4%).

Nine percent of respondents who reported drinking marijuana products in the past 30 days reported drinking marijuana products at least once per day, while 81% reported drinking marijuana products less than once per week.

All respondents who reported drinking marijuana products in the past 30 days were asked to indicate the amount of THC administered by drinking marijuana products over the past 30 days. The amount of THC reported by respondents should be interpreted with caution, as almost 1 in 5 respondents did not know how much THC they administered through drinking marijuana products. However, 60% of respondents reported administering between 1 and 150 mg of THC in the past 30 days by drinking marijuana products.

All respondents who reported drinking marijuana products in the past 30 days were asked to indicate the amount of CBD administered by drinking marijuana products over the past 30 days. The amount of CBD reported by respondents should be interpreted with caution, as approximately 1 in 4 respondents did not know how much CBD they administered through drinking marijuana products. However, 43% of respondents reported administering between 1 and 150 mg of CBD in the past 30 days through edible marijuana products. There were no significant differences in the amount of CBD administered by drinking marijuana products by gender, age, or education.

Table 11A: DPH Patient Drinking Marijuana Products by Gender (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Gender		
		Male (N=3251)	Female (N=2672)	p-value
Drank marijuana infused products in the past 30 days	6021			ns
No	5736 95.27	3086 94.92	2558 95.73	
Yes	285 4.73	165 5.08	114 4.27	
Frequency of drinking marijuana infused products †	258			ns
Less than once per week	209 81.01	117 80.14	86 81.13	
More than once per week (but not as much as once per day)	26 10.08	16 10.96	10 9.43	
Once per day	15 5.81	6 4.11	9 8.49	
Multiple times per day	8 3.10	7 4.79	1 0.94	
Amount of THC administered † ‡	277			ns
0 mg past 30 days	25 9.03	14 8.75	11 9.91	
Between 1 and 150 mg in past 30 days	166 59.93	93 58.13	67 60.36	
Between 151 and 300 mg in past 30 days	26 9.39	14 8.75	12 10.81	
More than 300 mg in past 30 days	4 1.44	3 1.88	1 0.90	
Don't know/not sure	56 20.22	36 22.50	20 18.02	
Amount of CBD administered † ‡	275			ns
0 mg past 30 days	71 25.82	45 28.13	25 22.94	
Between 1 and 150 mg in past 30 days	119 43.27	62 38.75	53 48.62	
Between 151 and 300 mg in past 30 days	12 4.36	6 3.75	6 5.50	
More than 300 mg in past 30 days	2 0.73	2 1.25	0 0.00	
Don't know/not sure	71 25.82	45 28.13	25 22.94	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 11B: DPH Patient Drinking Marijuana Products by Age Group (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Age Group		
		≤ 50 years (N=3179)	≥ 51 years (N=2748)	p-value
Drank marijuana infused products in the past 30 days	6021			****
No	5736 95.27	2976 93.61	2669 97.13	
Yes	285 4.73	203 6.39	79 2.87	
Frequency of drinking marijuana infused products †	258			**
Less than once per week	209 81.01	158 85.87	49 69.01	
More than once per week (but not as much as once per day)	26 10.08	17 9.24	9 12.68	
Once per day	15 5.81	5 2.72	10 14.08	
Multiple times per day	8 3.10	4 2.17	3 4.23	
Amount of THC administered † ‡	277			ns
0 mg past 30 days	25 9.03	17 8.59	8 10.53	
Between 1 and 150 mg in past 30 days	166 59.93	126 63.64	38 50.00	
Between 151 and 300 mg in past 30 days	26 9.39	19 9.60	7 9.21	
More than 300 mg in past 30 days	4 1.44	3 1.52	1 1.32	
Don't know/not sure	56 20.22	33 16.67	22 28.95	
Amount of CBD administered † ‡	275			ns
0 mg past 30 days	71 25.82	54 27.41	16 21.33	
Between 1 and 150 mg in past 30 days	119 43.27	88 44.67	30 40.00	
Between 151 and 300 mg in past 30 days	12 4.36	6 3.05	5 6.67	
More than 300 mg in past 30 days	2 0.73	1 0.51	1 1.33	
Don't know/not sure	71 25.82	48 24.37	23 30.67	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 11C: DPH Patient Drinking Marijuana Products by Education (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Education		
		< Bachelor's (N=2836)	≥ Bachelor's (N=3168)	p-value
Drank marijuana infused products in the past 30 days	6021			**
No	5736 95.27	2676 94.36	3043 96.05	
Yes	285 4.73	160 5.64	125 3.95	
Frequency of drinking marijuana infused products †	258			ns
Less than once per week	209 81.01	119 82.07	90 79.65	
More than once per week (but not as much as once per day)	26 10.08	12 8.28	14 12.39	
Once per day	15 5.81	10 6.90	5 4.42	
Multiple times per day	8 3.10	4 2.76	4 3.54	
Amount of THC administered † ‡	277			*
0 mg past 30 days	25 9.03	16 10.26	9 7.44	
Between 1 and 150 mg in past 30 days	166 59.93	85 54.49	81 66.94	
Between 151 and 300 mg in past 30 days	26 9.39	22 14.10	4 3.31	
More than 300 mg in past 30 days	4 1.44	2 1.28	2 1.65	
Don't know/not sure	56 20.22	31 19.87	25 20.66	
Amount of CBD administered † ‡	275			ns
0 mg past 30 days	71 25.82	41 26.62	30 24.79	
Between 1 and 150 mg in past 30 days	119 43.27	63 40.91	56 46.28	
Between 151 and 300 mg in past 30 days	12 4.36	10 6.49	2 1.65	
More than 300 mg in past 30 days	2 0.73	1 0.65	1 0.83	
Don't know/not sure	71 25.82	39 25.32	32 26.45	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Sublingual or Orally Administered Uptake Marijuana Products

Tables 12A, 12B, and 12C summarize results of survey responses pertaining to use of sublingual or orally administered uptake marijuana products, with comparisons by gender, age group, and educational attainment, respectively. 23% of respondents who reported using marijuana or marijuana products at least once in the past 30 days reported using sublingual or orally administered uptake marijuana products in the past 30 days. Using sublingual or orally administered uptake marijuana products was significantly higher among female respondents compared to male respondents (28% vs. 20%), respondents 51 years or older compared to younger respondents (26% vs. 22%) and respondents with a Bachelor's degree compared to respondents without a degree (25% vs. 22%).

Twenty-five percent of respondents who reported using sublingual or orally administered uptake marijuana products in the past 30 days reported using these products at least once per day, while 47% reported using these marijuana products less than once per week. A larger proportion of respondents over the age of 50 than younger respondents reported using sublingual or orally administered uptake marijuana products once per day (23% vs. 10%) and multiple times per day (10% vs. 6%).

All respondents who reported using sublingual or orally administered uptake marijuana products in the past 30 days were asked to indicate the amount of THC administered by using these products over the past 30 days. The amount of THC reported by respondents should be interpreted with caution, as almost 1 in 4 respondents did not know how much THC they administered through sublingual or orally administered uptake marijuana products. However, 54% of respondents reported administering between 1 and 150 mg of THC in the past 30 days through sublingual or orally administered uptake marijuana products.

All respondents who reported using sublingual or orally administered uptake marijuana products in the past 30 days were asked to indicate the amount of CBD administered by using these products over the past 30 days. The amount of CBD reported by respondents should be interpreted with caution, as 30% respondents did not know how much CBD they administered through sublingual or orally administered uptake marijuana products. However, 48% of respondents reported administering between 1 and 150 mg of THC in the past 30 days through sublingual or orally administered uptake marijuana products.

Table 12A: DPH Patient Survey Sublingual Marijuana Products by Gender (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Gender		
		Male (N=3251)	Female (N=2672)	p-value
Used sublingual/orally administered uptake products in the past 30 days	6021			****
No	4608 76.53	2600 79.98	1934 72.38	
Yes	1413 23.47	651 20.02	738 27.62	
Frequency of using sublingual or orally administered uptake products †	1337			ns
Less than once per week	634 47.42	296 48.13	324 46.42	
More than once per week (but not as much as once per day)	370 27.67	170 27.64	194 27.79	
Once per day	218 16.31	96 15.61	119 17.05	
Multiple times per day	115 8.60	53 8.62	61 8.74	
Amount of THC administered † ‡	1359			**
0 mg past 30 days	182 13.39	62 9.90	115 16.22	
Between 1 and 150 mg in past 30 days	728 53.57	354 56.55	361 50.92	
Between 151 and 300 mg in past 30 days	81 5.96	45 7.19	35 4.94	
More than 300 mg in past 30 days	22 1.62	14 2.24	8 1.13	
Don't know/not sure	346 25.46	151 24.12	190 26.80	
Amount of CBD administered † ‡	1371			*
0 mg past 30 days	154 11.23	84 13.35	63 8.77	
Between 1 and 150 mg in past 30 days	664 48.43	294 46.74	358 49.86	
Between 151 and 300 mg in past 30 days	108 7.88	51 8.11	56 7.80	
More than 300 mg in past 30 days	36 2.63	21 3.34	15 2.09	
Don't know/not sure	409 29.83	179 28.46	226 31.48	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Oral Capsules/Tablets

Tables 13A, 13B, and 13C summarize results of survey responses pertaining to use of oral capsules or tablets, with comparisons by gender, age group, and educational attainment, respectively. 11% of respondents reported using oral capsules/tablets in the past 30 days to administer marijuana. There were no significant differences in the proportion of respondents who reported using oral capsules/tablets by gender, age, or education.

Twenty-four percent of respondents reported using oral capsules/tablets at least once per day, while 56% reported using these marijuana products less than once per week.

All respondents who reported using oral capsules/tablets in the past 30 days were asked to indicate the amount of THC administered by using these products over the past 30 days. The amount of THC reported by respondents should be interpreted with caution, as almost 1 in 5 respondents did not know how much THC they administered through oral capsules/tablets. However, 55% of respondents reported administering between 1 and 150 mg of THC in the past 30 days through oral capsules/tablets, and 15% reported administering 0 mg of THC. There were no significant differences the amount of THC administered by using capsules/tablets by gender, age, or education.

All respondents who reported using oral capsules/tablets in the past 30 days were asked to indicate the amount of CBD administered by using these products over the past 30 days. The amount of CBD reported by respondents should be interpreted with caution, as almost 1 in 4 respondents did not know how much CBD they administered through oral capsules/tablets. However, 47% of respondents reported administering between 1 and 150 mg of CBD in the past 30 days through oral capsules/tablets, and 16% reported administering 0 mg of CBD.

Table 13A: DPH Patient Survey Oral Capsules and Tables by Gender (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Gender		
		Male (N=3251)	Female (N=2672)	p-value
Respondent used oral capsules/tablets (THC and/or CBD) in the past 30 days	6021			ns
No	5370 89.19	2898 89.14	2387 89.33	
Yes	651 10.81	353 10.86	285 10.67	
Frequency of using oral capsules/tablets in the past 30 days	595			ns
Less than once per week	331 55.63	177 55.66	147 55.47	
More than once per week (but not as much as once per day)	121 20.34	69 21.70	49 18.49	
Once per day	106 17.82	53 16.67	51 19.25	
Multiple times per day	37 6.22	19 5.97	18 6.79	
Amount of THC administered † ‡	623			ns
0 mg past 30 days	95 15.25	48 14.24	47 17.15	
Between 1 and 150 mg in past 30 days	345 55.38	187 55.49	151 55.11	
Between 151 and 300 mg in past 30 days	49 7.87	28 8.31	20 7.30	
More than 300 mg in past 30 days	15 2.41	12 3.56	2 0.73	
Don't know/not sure	119 19.1	62 18.40	54 19.71	
Amount of CBD administered † ‡	628			ns
0 mg past 30 days	103 16.40	57 16.76	45 16.30	
Between 1 and 150 mg in past 30 days	292 46.50	157 46.18	129 46.74	
Between 151 and 300 mg in past 30 days	56 8.92	27 7.94	29 10.51	
More than 300 mg in past 30 days	23 3.66	15 4.41	8 2.90	
Don't know/not sure	154 24.52	84 24.71	65 23.55	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 13B: DPH Patient Survey Oral Capsules and Tables by Age Group (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Age Group		
		≤ 50 years (N=3179)	≥ 51 years (N=2748)	p-value
Respondent used oral capsules/tablets (THC and/or CBD) in the past 30 days	6021			ns
No	5370 89.19	2822 88.77	2463 89.63	
Yes	651 10.81	357 11.23	285 10.37	
Frequency of using oral capsules/tablets in the past 30 days	595			**
Less than once per week	331 55.63	206 62.24	121 47.27	
More than once per week (but not as much as once per day)	121 20.34	59 17.82	60 23.44	
Once per day	106 17.82	49 14.80	55 21.48	
Multiple times per day	37 6.22	17 5.14	20 7.81	
Amount of THC administered † ‡	623			ns
0 mg past 30 days	95 15.25	51 14.83	44 16.24	
Between 1 and 150 mg in past 30 days	345 55.38	192 55.81	147 54.24	
Between 151 and 300 mg in past 30 days	49 7.87	34 9.88	14 5.17	
More than 300 mg in past 30 days	15 2.41	9 2.62	6 2.21	
Don't know/not sure	119 19.1	58 16.86	60 22.14	
Amount of CBD administered † ‡	628			*
0 mg past 30 days	103 16.40	61 17.68	39 14.18	
Between 1 and 150 mg in past 30 days	292 46.50	169 48.99	119 43.27	
Between 151 and 300 mg in past 30 days	56 8.92	34 9.86	22 8.00	
More than 300 mg in past 30 days	23 3.66	8 2.32	15 5.45	
Don't know/not sure	154 24.52	73 21.16	80 29.09	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 13C: DPH Patient Survey Oral Capsules and Tables by Education (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Education		
		< Bachelor's (N=2836)	≥ Bachelor's (N=3168)	p-value
Respondent used oral capsules/tablets (THC and/or CBD) in the past 30 days	6021			*
No	5370 89.19	2559 90.23	2795 88.23	
Yes	651 10.81	277 9.77	373 11.77	
Frequency of using oral capsules/tablets in the past 30 days	595			ns
Less than once per week	331 55.63	133 52.99	197 57.43	
More than once per week (but not as much as once per day)	121 20.34	49 19.52	72 20.99	
Once per day	106 17.82	46 18.33	60 17.49	
Multiple times per day	37 6.22	23 9.16	14 4.08	
Amount of THC administered † ‡	623			ns
0 mg past 30 days	95 15.25	37 14.02	58 16.20	
Between 1 and 150 mg in past 30 days	345 55.38	136 51.52	208 58.10	
Between 151 and 300 mg in past 30 days	49 7.87	29 10.98	20 5.59	
More than 300 mg in past 30 days	15 2.41	6 2.27	9 2.51	
Don't know/not sure	119 19.1	56 21.21	63 17.60	
Amount of CBD administered † ‡	628			ns
0 mg past 30 days	103 16.40	40 14.98	62 17.22	
Between 1 and 150 mg in past 30 days	292 46.50	122 45.69	170 47.22	
Between 151 and 300 mg in past 30 days	56 8.92	27 10.11	29 8.06	
More than 300 mg in past 30 days	23 3.66	11 4.12	12 3.33	
Don't know/not sure	154 24.52	67 25.09	87 24.17	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Topical Cannabis, Oil, Ointment, Lotion, Salve

Tables 14A, 14B, and 14C summarize results of survey responses pertaining to applying topical cannabis, oil, ointment, lotion, salve, or other marijuana products to the skin, with comparisons by gender, age group, and educational attainment, respectively. 27% of respondents who reported using marijuana at least once in the past 30 days reported applying topical cannabis to the skin in the past 30 days. A significantly larger proportion of female respondents compared to males report applying topical cannabis (35% vs. 20%).

Twenty-six percent of respondents who reported using topical cannabis in the past 30 days reported applying topical cannabis to the skin at least once per day, while 42% reported applying topical cannabis less than once per week. A larger proportion of respondents without a Bachelor's degree than respondents with a degree reported applying topical cannabis to the skin multiple times per day (14% vs. 7%), while a larger proportion of respondents with a Bachelor's degree than without reported applying topical cannabis to the skin less than once per week (46% vs. 36%).

All respondents who reported applying topical cannabis, oil, ointment, lotion, salve, etc. to the skin in the past 30 days were asked to indicate the amount of THC administered by using these products over the past 30 days. The amount of THC reported by respondents should be interpreted with caution, as more than 2 in 5 respondents did not know how much THC they administered through topical cannabis. However, 38% of respondents reported administering between 1 and 150 mg of THC in the past 30 days through topical cannabis, and 13% reported administering 0 mg of THC. A larger proportion of male respondents than female reported administering between 1 and 150 mg of topical cannabis to the skin (46% vs. 33%), while a larger proportion of females than males did not know how much THC they administered through topical cannabis (49% vs. 38%).

All respondents who reported applying topical cannabis, oil, ointment, lotion, salve, etc. to the skin in the past 30 days were asked to indicate the amount of CBD administered by using these products over the past 30 days. The amount of CBD reported by respondents should be interpreted with caution, as almost one half of all respondents did not know how much CBD they administered through topical cannabis. However, 42% of respondents reported administering between 1 and 150 mg of CBD in the past 30 days through topical cannabis.

Table 14A: DPH Patient Survey Topical Marijuana by Gender (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Gender		
		Male (N=3251)	Female (N=2672)	p-value
Respondent applied topical marijuana to skin in the past 30 days	6021			****
No	4421 73.43	2613 80.38	1739 65.08	
Yes	1600 26.57	638 19.62	933 34.92	
Frequency of applying topical marijuana to skin	1513			***
Less than once per week	628 41.51	271 45.55	344 38.65	
More than once per week (but not as much as once per day)	494 32.65	195 32.77	293 32.92	
Once per day	229 15.14	88 14.79	136 15.28	
Multiple times per day	162 10.71	41 6.89	117 13.15	
Amount of THC administered † ‡	1554			****
0 mg past 30 days	205 13.19	71 11.45	130 14.35	
Between 1 and 150 mg in past 30 days	593 38.16	284 45.81	298 32.89	
Between 151 and 300 mg in past 30 days	57 3.67	27 4.35	28 3.09	
More than 300 mg in past 30 days	10 0.64	3 0.48	6 0.66	
Don't know/not sure	689 44.34	235 37.90	444 49.01	
Amount of CBD administered † ‡	1557			***
0 mg past 30 days	103 6.62	40 6.43	60 6.62	
Between 1 and 150 mg in past 30 days	656 42.13	299 48.07	344 37.93	
Between 151 and 300 mg in past 30 days	70 4.50	31 4.98	36 3.97	
More than 300 mg in past 30 days	10 0.64	3 0.48	7 0.77	
Don't know/not sure	718 46.11	249 40.03	460 50.72	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 14B: DPH Patient Survey Topical Marijuana by Age Group (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Age Group		
		≤ 50 years (N=3179)	≥ 51 years (N=2748)	p-value
Respondent applied topical marijuana to skin in the past 30 days	6021			*
No	4421 73.43	2376 74.74	1978 71.98	
Yes	1600 26.57	803 25.26	770 28.02	
Frequency of applying topical marijuana to skin	1513			***
Less than once per week	628 41.51	355 46.65	261 35.80	
More than once per week (but not as much as once per day)	494 32.65	238 31.27	252 34.57	
Once per day	229 15.14	94 12.35	130 17.83	
Multiple times per day	162 10.71	74 9.72	86 11.80	
Amount of THC administered † ‡	1554			*
0 mg past 30 days	205 13.19	99 12.68	103 13.79	
Between 1 and 150 mg in past 30 days	593 38.16	323 41.36	259 34.67	
Between 151 and 300 mg in past 30 days	57 3.67	34 4.35	22 2.95	
More than 300 mg in past 30 days	10 0.64	6 0.77	4 0.54	
Don't know/not sure	689 44.34	319 40.85	359 48.06	
Amount of CBD administered † ‡	1557			***
0 mg past 30 days	103 6.62	52 6.68	50 6.65	
Between 1 and 150 mg in past 30 days	656 42.13	361 46.34	283 37.63	
Between 151 and 300 mg in past 30 days	70 4.50	41 5.26	28 3.72	
More than 300 mg in past 30 days	10 0.64	7 0.90	3 0.40	
Don't know/not sure	718 46.11	318 40.82	388 51.60	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 14C: DPH Patient Survey Topical Marijuana by Education (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Education		
		< Bachelor's (N=2836)	≥ Bachelor's (N=3168)	p-value
Respondent applied topical marijuana to skin in the past 30 days	6021			ns
No	4421 73.43	2075 73.17	2333 73.64	
Yes	1600 26.57	761 26.83	835 26.36	
Frequency of applying topical marijuana to skin	1513			****
Less than once per week	628 41.51	256 36.26	370 46.02	
More than once per week (but not as much as once per day)	494 32.65	239 33.85	255 31.72	
Once per day	229 15.14	109 15.44	120 14.93	
Multiple times per day	162 10.71	102 14.45	59 7.34	
Amount of THC administered † ‡	1554			***
0 mg past 30 days	205 13.19	86 11.72	119 14.57	
Between 1 and 150 mg in past 30 days	593 38.16	272 37.06	320 39.17	
Between 151 and 300 mg in past 30 days	57 3.67	43 5.86	13 1.59	
More than 300 mg in past 30 days	10 0.64	5 0.68	5 0.61	
Don't know/not sure	689 44.34	328 44.69	360 44.06	
Amount of CBD administered † ‡	1557			**
0 mg past 30 days	103 6.62	54 7.32	48 5.89	
Between 1 and 150 mg in past 30 days	656 42.13	296 40.11	359 44.05	
Between 151 and 300 mg in past 30 days	70 4.50	47 6.37	22 2.70	
More than 300 mg in past 30 days	10 0.64	6 0.81	4 0.49	
Don't know/not sure	718 46.11	335 45.39	382 46.87	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Rectal/Vaginal Cannabis

Tables 15A, 15B, and 15C summarize results of survey responses pertaining to using rectal/vaginal cannabis, with comparisons by gender, age group, and educational attainment, respectively. 1% of respondents who reported marijuana or marijuana product use at least once in the past 30 days reported using rectal/vaginal cannabis in the past 30 days. There were no significant differences in the proportion of respondents who reported use of rectal/vaginal cannabis by gender, age, or education.

Eighty-nine percent of respondents who reported using rectal/vaginal cannabis in the past 30 days reported using rectal/vaginal cannabis less than once per week. There were no significant differences in the frequency of rectal/vaginal cannabis use by gender, age, or education.

All respondents who reported using rectal/vaginal cannabis in the past 30 days were asked to indicate the amount of THC administered by using these products over the past 30 days. The amount of THC reported by respondents should be interpreted with caution, as almost 1 in 5 did not know how much THC they administered through rectal/vaginal cannabis. However, 70% of respondents reported administering between 1 and 150 mg of THC in the past 30 days through rectal/vaginal cannabis. There were no significant differences in the amount of THC administered by using rectal/vaginal cannabis by gender, age, or education.

All respondents who reported using rectal/vaginal cannabis in the past 30 days were asked to indicate the amount of CBD administered by using these products over the past 30 days. The amount of CBD reported by respondents should be interpreted with caution, as almost one third of all respondents did not know how much CBD they administered through rectal/vaginal cannabis. However, 39% of respondents reported administering between 1 and 150 mg of CBD in the past 30 days through rectal/vaginal cannabis, while 24% reported administering 0 mg. There were no significant differences in the amount of CBD administered by using rectal/vaginal cannabis by gender, age, or education.

Table 15A: DPH Patient Survey Rectal/Vaginal Marijuana by Gender (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Gender		
		Male (N=3293)	Female (N=2720)	p-value
Respondent used rectal/vaginal cannabis in the past 30 days	6021			ns
No	5946 98.75	3219 99.02	2633 98.54	
Yes	75 1.25	32 0.98	39 1.46	
Frequency of using rectal/vaginal cannabis in the past 30 days	66			ns
Less than once per week	58 87.88	23 82.14	33 91.67	
More than once per week (but not as much as once per day)	3 4.55	1 3.57	2 5.56	
Once per day	2 3.03	1 3.57	1 2.78	
Multiple times per day	3 4.55	3 10.71	0 0.00	
Amount of THC administered † ‡	69			ns
0 mg past 30 days	3 4.35	1 3.45	1 2.70	
Between 1 and 150 mg in past 30 days	48 69.57	19 65.52	27 72.97	
Between 151 and 300 mg in past 30 days	4 5.80	3 10.34	1 2.70	
More than 300 mg in past 30 days	1 1.45	1 3.45	0 0.00	
Don't know/not sure	13 18.84	5 17.24	8 21.62	
Amount of CBD administered † ‡	70			ns
0 mg past 30 days	17 24.29	4 13.79	12 31.58	
Between 1 and 150 mg in past 30 days	27 38.57	12 41.38	13 34.21	
Between 151 and 300 mg in past 30 days	3 4.29	2 6.90	1 2.63	
More than 300 mg in past 30 days	0 0.00	0 0.00	0 0.00	
Don't know/not sure	23 32.86	11 37.93	12 31.58	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 15B: DPH Patient Survey Rectal/Vaginal Marijuana by Age Group (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Age Group		
		≤ 50 years (N=3224)	≥ 51 years (N=2793)	p-value
Respondent used rectal/vaginal cannabis in the past 30 days	6021			ns
No	5946 98.75	3131 98.49	2722 99.05	
Yes	75 1.25	48 1.51	26 0.95	
Frequency of using rectal/vaginal cannabis in the past 30 days	66			ns
Less than once per week	58 87.88	41 95.35	17 73.91	
More than once per week (but not as much as once per day)	3 4.55	1 2.33	2 8.70	
Once per day	2 3.03	0 0.00	2 8.70	
Multiple times per day	3 4.55	1 2.33	2 8.70	
Amount of THC administered † ‡	69			ns
0 mg past 30 days	3 4.35	2 4.44	1 4.17	
Between 1 and 150 mg in past 30 days	48 69.57	33 73.33	15 62.50	
Between 151 and 300 mg in past 30 days	4 5.80	2 4.44	2 8.33	
More than 300 mg in past 30 days	1 1.45	0 0.00	1 4.17	
Don't know/not sure	13 18.84	8 17.78	5 20.83	
Amount of CBD administered † ‡	70			ns
0 mg past 30 days	17 24.29	11 24.44	6 24.00	
Between 1 and 150 mg in past 30 days	27 38.57	18 40.00	9 36.00	
Between 151 and 300 mg in past 30 days	3 4.29	3 6.67	0 0.00	
More than 300 mg in past 30 days	0 0.00	0 0.00	0 0.00	
Don't know/not sure	23 32.86	13 28.89	10 40.00	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 15C: DPH Patient Survey Rectal/Vaginal Marijuana by Education (Among 6,111 Respondents who Used Marijuana in Past 30 Days)

	Total N %	Education		
		< Bachelor's (N=2871)	≥ Bachelor's (N=3223)	p-value
Respondent used rectal/vaginal cannabis in the past 30 days	6021			ns
No	5946 98.75	2802 98.80	3127 98.71	
Yes	75 1.25	34 1.20	41 1.29	
Frequency of using rectal/vaginal cannabis in the past 30 days	66			ns
Less than once per week	58 87.88	25 83.33	33 91.67	
More than once per week (but not as much as once per day)	3 4.55	3 10.00	0 0.00	
Once per day	2 3.03	1 3.33	1 2.78	
Multiple times per day	3 4.55	1 3.33	2 5.56	
Amount of THC administered † ‡	69			ns
0 mg past 30 days	3 4.35	1 3.33	2 5.13	
Between 1 and 150 mg in past 30 days	48 69.57	22 73.33	26 66.67	
Between 151 and 300 mg in past 30 days	4 5.80	0 0.00	4 10.26	
More than 300 mg in past 30 days	1 1.45	0 0.00	1 2.56	
Don't know/not sure	13 18.84	7 23.33	6 15.38	
Amount of CBD administered † ‡	70			ns
0 mg past 30 days	17 24.29	5 16.67	12 30.00	
Between 1 and 150 mg in past 30 days	27 38.57	13 43.33	14 35.00	
Between 151 and 300 mg in past 30 days	3 4.29	2 6.67	1 2.50	
More than 300 mg in past 30 days	0 0.00	0 0.00	0 0.00	
Don't know/not sure	23 32.86	10 33.33	13 32.50	
† Among respondents reporting using vaporized marijuana concentrate in the past 30 days ‡ Total monthly amount consumed *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Perceptions of Medical Marijuana Use

All respondents, regardless of their use of marijuana in the past 30 days, were asked to report on various perceptions and behavior related to medical use of marijuana. Results are summarized in *Tables 16A, 16B, and 16C*, with comparisons by gender, age group, and educational attainment, respectively.

Sixty-six percent of survey respondents reported using marijuana or marijuana products for medical purposes for at least a year, with 20% reporting use for over 3 years. 7% of respondents reported medical use of marijuana or marijuana products for 3 months or less. A larger proportion of male respondents than female reported medical use for at least 3 years (21% vs. 16%), while a larger proportion of respondents under the age of 51 compared to older respondents reported medical use for at least 3 years (22% vs. 16%). Finally, a larger proportion of respondents without a Bachelor's degree than with reported medical use for at least 3 years (22% vs. 17%).

Ninety-four percent of survey respondents reported feeling safe or very safe when buying medical marijuana products at a licensed dispensary, while 5% reported feeling very unsafe. A larger proportion of respondents over the age of 50 than younger respondents reported feeling very unsafe (7% vs. 4%), while a larger proportion of younger respondents than older reported feeling very safe (89% vs. 86%). A larger proportion of respondents without a Bachelor's degree than with a degree reported feeling very unsafe (7% vs. 4%), while a larger proportion of respondents with a Bachelor's degree than without reported feeling very safe (90% vs. 85%).

Sixty-six percent of survey respondents reported somewhat high or very high knowledge of products when selecting products for medical use, while 7% reported somewhat low or very low knowledge. A larger proportion of male respondents than female reported very high knowledge (42% vs. 32%), while a larger proportion of female respondents than male reported average knowledge (31% vs. 23%). A larger proportion of respondents under the age of 51 than older respondents report very high knowledge (43% vs 32%), while a larger proportion of older respondents than younger report average knowledge (29% vs. 24%).

Eighty-nine percent of survey respondents indicated that they had somewhat high or very high confidence that they were receiving safe, uncontaminated products at licensed dispensaries, while less than 2% reported that they had somewhat low or very low confidence. A larger proportion of respondents younger than 51 compared to older respondents reported very high confidence (71% vs. 67%), while a larger proportion of older respondents reported average confidence (11% vs. 8%). A larger proportion of respondents with a Bachelor's degree than without a degree reported very high confidence in receiving safe, uncontaminated products (71% vs. 68%).

Ninety-one percent of survey respondents reported that marijuana use has been effective or very effective in treating their medical condition, while 2% reported that marijuana use has had little effect or no effect at all. A larger proportion of male respondents than female reported that marijuana use has been effective (27% vs. 24%).

A larger proportion of respondents less than 51 years old than older respondents reported that marijuana use has been very effective (72% vs. 58%), while a larger proportion of older respondents than younger reported that marijuana use has been effective (30% vs. 22%) or somewhat effective (10% vs. 5%).

Table 16A: DPH Patient Survey Perceptions of Medical Use of Marijuana by Gender (Among All 6,934 Respondents)

	Total N %	Gender		
		Male (N=3732)	Female (N=3056)	p-value
Length of time using marijuana or marijuana products for medical purposes	6574			****
0-3 months	466 7.09	223 6.31	238 8.12	
3-6 months	675 10.27	341 9.65	324 11.05	
6-12 months	1124 17.10	584 16.53	522 17.80	
1-3 years	3051 46.41	1633 46.22	1365 46.56	
3+ years	1258 19.14	752 21.29	483 16.47	
When you buy medical marijuana at a licensed dispensary, how do you feel about your personal safety?	6552			ns
Very unsafe	340 5.19	186 5.28	150 5.13	
Somewhat unsafe	61 0.93	34 0.97	26 0.89	
Somewhat safe	408 6.23	221 6.28	182 6.22	
Very safe	5743 87.65	3079 87.47	2566 87.76	
When selecting a marijuana product for your medical use, how would you rate your current knowledge of the recommended product based on information provided by your certified practitioner?	6461			****
Very low	159 2.46	65 1.87	90 3.13	
Somewhat low	306 4.74	138 3.97	166 5.77	
Average	1734 26.84	796 22.88	906 31.49	
Somewhat high	1825 28.25	1015 29.18	784 27.25	
Very high	2437 37.72	1465 42.11	931 32.36	
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

(Continued) Table 16A: DPH Patient Survey Perceptions of Medical Use of Marijuana by Gender (Among All 6,934 Respondents)

	Total N %	Gender		
		Male (N=3732)	Female (N=3056)	p-value
When purchasing marijuana or marijuana products at a licensed dispensary, how confident do you feel that you are receiving a safe, uncontaminated product?	6538			ns
Very low confidence	41 0.63	22 0.63	17 0.58	
Low confidence	79 1.21	45 1.28	33 1.13	
Average confidence	613 9.38	322 9.15	280 9.62	
Somewhat high confidence	1266 19.36	727 20.65	520 17.86	
Very high confidence	4539 69.42	2404 68.30	2062 70.81	
How effective do you feel marijuana or marijuana products have been in treating the medical condition for which you are using it?	6551			****
Not effective at all	40 0.61	16 0.45	23 0.79	
A little effective	92 1.40	37 1.05	55 1.88	
Somewhat effective	465 7.10	222 6.31	235 8.04	
Effective	1678 25.61	960 27.27	693 23.70	
Very effective	4276 65.27	2285 64.91	1918 65.60	

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

Table 16B: DPH Patient Survey Perceptions of Medical Use of Marijuana by Age Group (Among All 6,934 Respondents)

	Total N %	Age Group		
		≤ 50 years (N=3584)	≥ 51 years (N=3188)	p-value
Length of time using marijuana or marijuana products for medical purposes	6574			****
0-3 months	466 7.09	232 6.79	225 7.40	
3-6 months	675 10.27	365 10.68	301 9.90	
6-12 months	1124 17.10	578 16.91	523 17.20	
1-3 years	3051 46.41	1498 43.83	1499 49.29	
3+ years	1258 19.14	745 21.80	493 16.21	
When you buy medical marijuana at a licensed dispensary, how do you feel about your personal safety?	6552			****
Very unsafe	340 5.19	122 3.59	207 6.81	
Somewhat unsafe	61 0.93	34 1.00	26 0.86	
Somewhat safe	408 6.23	220 6.47	183 6.02	
Very safe	5743 87.65	3023 88.94	2623 86.31	
When selecting a marijuana product for your medical use, how would you rate your current knowledge of the recommended product based on information provided by your certified practitioner?	6461			****
Very low	159 2.46	58 1.74	98 3.26	
Somewhat low	306 4.74	109 3.26	188 6.25	
Average	1734 26.84	810 24.25	885 29.43	
Somewhat high	1825 28.25	918 27.49	879 29.23	
Very high	2437 37.72	1445 43.26	957 31.83	
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

(Continued) Table 16B: DPH Patient Survey Perceptions of Medical Use of Marijuana by Gender (Among All 6,934 Respondents)

	Total N %	Age Group		
		≤ 50 years (N=3584)	≥ 51 years (N=3188)	p-value
When purchasing marijuana or marijuana products at a licensed dispensary, how confident do you feel that you are receiving a safe, uncontaminated product?	6538			****
Very low confidence	41 0.63	25 0.73	14 0.46	
Low confidence	79 1.21	51 1.50	27 0.89	
Average confidence	613 9.38	261 7.67	342 11.33	
Somewhat high confidence	1266 19.36	641 18.84	610 20.21	
Very high confidence	4539 69.42	2425 71.26	2026 67.11	
How effective do you feel marijuana or marijuana products have been in treating the medical condition for which you are using it?	6551			****
Not effective at all	40 0.61	7 0.21	32 1.06	
A little effective	92 1.40	39 1.15	49 1.62	
Somewhat effective	465 7.10	159 4.67	296 9.77	
Effective	1678 25.61	762 22.37	896 29.57	
Very effective	4276 65.27	2439 71.61	1757 57.99	

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

Table 16C: DPH Patient Survey Perceptions of Medical Use of Marijuana by Education (Among All 6,934 Respondents)

	Total N %	Education		
		< Bachelor's (N=3282)	≥ Bachelor's (N=3595)	p-value
Length of time using marijuana or marijuana products for medical purposes	6574			****
0-3 months	466 7.09	200 6.40	263 7.67	
3-6 months	675 10.27	304 9.73	368 10.73	
6-12 months	1124 17.10	505 16.16	619 18.04	
1-3 years	3051 46.41	1432 45.82	1610 46.93	
3+ years	1258 19.14	684 21.89	571 16.64	
When you buy medical marijuana at a licensed dispensary, how do you feel about your personal safety?	6552			****
Very unsafe	340 5.19	210 6.76	129 3.76	
Somewhat unsafe	61 0.93	33 1.06	27 0.79	
Somewhat safe	408 6.23	223 7.18	183 5.34	
Very safe	5743 87.65	2639 84.99	3091 90.12	
When selecting a marijuana product for your medical use, how would you rate your current knowledge of the recommended product based on information provided by your certified practitioner?	6461			***
Very low	159 2.46	66 2.15	91 2.69	
Somewhat low	306 4.74	145 4.73	161 4.76	
Average	1734 26.84	839 27.38	889 26.31	
Somewhat high	1825 28.25	791 25.82	1029 30.45	
Very high	2437 37.72	1223 39.92	1209 35.78	
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

(Continued) Table 16C: DPH Patient Survey Perceptions of Medical Use of Marijuana by Education (Among All 6,934 Respondents)

	Total N %	Education		
		< Bachelor's (N=3282)	≥ Bachelor's (N=3595)	p-value
When purchasing marijuana or marijuana products at a licensed dispensary, how confident do you feel that you are receiving a safe, uncontaminated product?	6538			****
Very low confidence	41 0.63	27 0.87	13 0.38	
Low confidence	79 1.21	39 1.26	40 1.17	
Average confidence	613 9.38	348 11.20	264 7.73	
Somewhat high confidence	1266 19.36	590 18.99	672 19.68	
Very high confidence	4539 69.42	2103 67.69	2425 71.03	
How effective do you feel marijuana or marijuana products have been in treating the medical condition for which you are using it?	6551			***
Not effective at all	40 0.61	20 0.64	20 0.58	
A little effective	92 1.40	34 1.09	58 1.69	
Somewhat effective	465 7.10	193 6.21	270 7.89	
Effective	1678 25.61	756 24.31	919 26.85	
Very effective	4276 65.27	2107 67.75	2156 62.99	

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

Driving Issues Related to Marijuana Use

All survey respondents were asked to report on their driving behaviors related to marijuana use. Results are summarized in *Tables 17A, 17B, and 17C*, with comparisons by gender, age group, and educational attainment, respectively.

Ten percent of survey respondents indicated that in the past 30 days they had driven or operated a car or other motor vehicle while under the influence of marijuana or marijuana products. A larger proportion of respondents without a Bachelor's degree than with a degree reported driving while impaired (11% vs. 10%).

Eleven percent of survey respondents indicated that in the past 30 days they had ridden as a passenger in a car or other motor vehicle while the driver was under the influence of marijuana or marijuana products. A significantly larger proportion of respondents under age 51 compared to over 50 (14% vs. 7%) reported riding as a passenger with an

impaired driver in the past 30 days, as did a larger proportion of respondents without a Bachelor's degree compared to with a degree (13% vs. 9%).

Table 17A: DPH Patient Survey Driving Issued Related to Marijuana Use by Gender (Among All 6,934 Respondents)

	Total N %	Gender		
		Male (N=3732)	Female (N=3056)	p-value
During the past 30 days, how many times did you <u>drive/operate</u> a car or other motor vehicle when you were under the influence of (impaired from) marijuana or marijuana products?	6311			*
0 times	5472 86.71	2900 85.88	2489 87.73	
At least once	656 10.39	383 11.34	262 9.24	
Don't know/not sure	183 2.90	94 2.78	86 3.03	
During the past 30 days, how many times did you <u>ride as a passenger</u> in a car or other motor vehicle when the driver was under the influence of (impaired from) marijuana or marijuana products?	6414			ns
0 times	5486 85.53	2939 85.56	2463 85.58	
At least once	681 10.62	368 10.71	303 10.53	
Don't know/not sure	247 3.85	128 3.73	112 3.89	
<i>*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant</i>				

Table 17B: DPH Patient Survey Driving Issued Related to Marijuana Use by Age Group (Among All 6,934 Respondents)

	Total N %	Age Group		p-value
		≤ 50 years (N=3584)	≥ 51 years (N=3188)	
During the past 30 days, how many times did you <u>drive/operate</u> a car or other motor vehicle when you were under the influence of (impaired from) marijuana or marijuana products?	6311			**
0 times	5472 86.71	2766 85.27	2612 88.30	
At least once	656 10.39	377 11.62	270 9.13	
Don't know/not sure	183 2.90	101 3.11	76 2.57	
During the past 30 days, how many times did you <u>ride as a passenger</u> in a car or other motor vehicle when the driver was under the influence of (impaired from) marijuana or marijuana products?	6414			****
0 times	5486 85.53	2687 81.45	2700 89.91	
At least once	681 10.62	465 14.10	207 6.89	
Don't know/not sure	247 3.85	147 4.46	96 3.20	
<i>*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant</i>				

Table 17C: DPH Patient Survey Driving Issued Related to Marijuana Use by Education (Among All 6,934 Respondents)

	Total N %	Education		
		< Bachelor's (N=3282)	≥ Bachelor's (N=3595)	p-value
During the past 30 days, how many times did you <u>drive/operate</u> a car or other motor vehicle when you were under the influence of (impaired from) marijuana or marijuana products?	6311			****
0 times	5472 86.71	2548 84.96	2912 88.35	
At least once	656 10.39	336 11.20	317 9.62	
Don't know/not sure	183 2.90	115 3.83	67 2.03	
During the past 30 days, how many times did you <u>ride as a passenger</u> in a car or other motor vehicle when the driver was under the influence of (impaired from) marijuana or marijuana products?	6414			****
0 times	5486 85.53	2505 82.35	2968 88.44	
At least once	681 10.62	393 12.92	286 8.52	
Don't know/not sure	247 3.85	144 4.73	102 3.04	

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

Other Issues Related to Marijuana Use

All respondents were asked a series of questions pertaining to outcomes and consequences related to marijuana use, as well as other issues related to marijuana use. Results are summarized in *Tables 18A, 18B, and 18C*, with comparisons by gender, age group, and educational attainment, respectively.

All survey respondents were asked to choose from a list negative outcomes/consequences related to their marijuana use. 83% of respondents reported experiencing no negative outcomes related to marijuana use. A significantly larger proportion of respondents over the age of 51 than under reported no negative outcomes related to marijuana use (86% vs 80%). A significantly larger proportion of respondents under the age of 51 than over reported negative occupational/job-related issues related to marijuana use (1% vs. 0%). A significantly larger proportion of respondents with a Bachelor's degree than without a degree reported negative changes in cognition related to marijuana use (8% vs. 5%).

All survey respondents were asked to choose from a list of positive outcomes/consequences related to their marijuana use. 78% reported positive changes in mood or mental health, 67% reported improved physical health, 30% reported positive changes in cognition, 41% reported positive changes in social relationships,

and 3% reported no positive outcomes or consequences. A significantly larger proportion of respondents younger than 51 years old reported positive changes in mood or mental health (87% vs. 70%), positive changes in cognition (37% vs. 22%) and positive changes in social relationships (52% vs. 29%). A larger proportion of respondents older than 50 years old reported no positive outcomes (4% vs. 2%). A significantly larger proportion of respondents without a Bachelor's degree than with a degree reported positive changes in cognition (35% vs. 25%) and positive changes in social relationships (46% vs. 38%).

Less than 1% of survey respondents indicated being treated in an emergency room or urgent care facility for reasons related to marijuana use. 14% of respondents who have used marijuana or marijuana products for medical purposes for at least 6 months reported needing to consume larger amounts of marijuana in the past 12 months in order to feel the same effects. A significantly larger proportion of respondents under the age of 51 than older respondents reported needing to consume larger amounts (19% vs. 8%).

Eighteen percent of respondents who have used marijuana or marijuana products for medical purposes for at least 6 months reported trying to cut down on their use of marijuana in the past 12 months. A significantly larger proportion of male respondents than female reported trying to cut down on their use of marijuana (20% vs. 16%), and a larger proportion of respondents under the age of 51 than older respondents reported trying to cut down their use of marijuana (23% vs. 13%). 9% of respondents have used marijuana or marijuana products for medical purposes for at least 6 months and who indicated trying to cut down on their marijuana use in the past 12 months reported feeling sick or experiencing withdrawal symptoms because of reduced marijuana use. There were no significant differences by gender, age, or education.

Table 18A: DPH Patient Survey Other Issues Related to Marijuana Use by Gender (Among All 6,934 Respondents)

	Total N %	Gender		
		Male (N=3732)	Female (N=3056)	p-value
Have you noticed any of the following <i>negative</i> outcomes/consequences related to your marijuana use?	6572			
Negative changes in mood or mental health	141 2.15	65 1.84	71 2.42	ns
Reduction in physical health	57 0.87	27 0.76	28 0.96	ns
Negative changes in cognition	435 6.62	223 6.32	191 6.52	ns
Negative changes in social relationships	75 1.14	52 1.47	22 0.75	**
Occupation/job-related issues	58 0.88	43 1.22	14 0.48	**
Other outcomes/consequences	370 5.63	178 5.04	183 6.24	*
No negative outcomes/consequences	5452 82.96	2952 83.63	2426 82.77	ns
Have you noticed any of the following <i>positive</i> outcomes/consequences related to your marijuana use?	6572			
Positive changes in mood or mental health	5158 78.48	2804 79.43	2261 77.14	*
Improved physical health	4435 67.48	2354 66.69	2010 68.58	ns
Positive changes in cognition	1979 30.11	1109 31.42	823 28.08	**
Positive changes in social relationships	2717 41.34	1509 42.75	1145 39.07	**
Other outcomes/consequences	1005 15.29	492 13.94	487 16.62	**
No positive outcomes/consequences	168 2.56	84 2.38	82 2.80	ns

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$; ns=not significant

Table 18A: DPH Patient Survey Other Issues Related to Marijuana Use by Gender (Among the 5433 Respondents who have Used Medical Use of Marijuana or Marijuana Products for at least 6 Months)

	Total N %	Gender		
		Male (N=3732)	Female (N=3056)	p-value
Treated in an emergency room or urgent care facility for any reason related to marijuana or marijuana product use?	6499			ns
0 times	6492 99.89	3486 99.89	2901 99.90	
At least once	7 0.11	4 0.11	3 0.10	
In the past 12 months, have you needed to consume larger amounts of marijuana or marijuana products in order to feel the same effects?	5011			ns
No	4313 86.07	2381 86.55	1864 85.62	
Yes	698 13.93	370 13.45	313 14.38	
In the past 12 months, have you tried to cut down on your marijuana or marijuana product use?	5010			****
No	4094 81.72	2187 79.76	1847 84.18	
Yes	916 18.28	555 20.24	347 15.82	
In the past 12 months, have you felt sick or had withdrawal symptoms because you stopped or cut down on your marijuana or marijuana product use? †	863			ns
No	786 91.08	472 90.08	300 92.59	
Yes	77 8.92	52 9.92	24 7.41	

† Among respondents who reported trying to cut down on marijuana or marijuana product use in the past 12 months

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

Table 18B: DPH Patient Survey Other Issues Related to Marijuana Use by Age Group (Among All 6,934 Respondents)

	Total N %	Age Group		
		≤ 50 years (N=3584)	≥ 51 years (N=3188)	p-value
Have you noticed any of the following <i>negative</i> outcomes/consequences related to your marijuana use?	6572			
Negative changes in mood or mental health	141 2.15	92 2.70	48 1.58	**
Reduction in physical health	57 0.87	40 1.17	17 0.56	**
Negative changes in cognition	435 6.62	257 7.54	174 5.71	**
Negative changes in social relationships	75 1.14	45 1.32	30 0.98	ns
Occupation/job-related issues	58 0.88	45 1.32	12 0.39	****
Other outcomes/consequences	370 5.63	208 6.10	156 5.12	ns
No negative outcomes/consequences	5452 82.96	2741 80.40	2611 85.72	****
Have you noticed any of the following <i>positive</i> outcomes/consequences related to your marijuana use?	6572			
Positive changes in mood or mental health	5158 78.48	2955 86.68	2123 69.70	****
Improved physical health	4435 67.48	2330 68.35	2033 66.74	ns
Positive changes in cognition	1979 30.11	1266 37.14	678 22.26	****
Positive changes in social relationships	2717 41.34	1784 52.33	891 29.25	****
Other outcomes/consequences	1005 15.29	441 12.94	551 18.09	****
No positive outcomes/consequences	168 2.56	53 1.55	112 3.68	****

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$; ns=not significant

(Continued) Table 18B: DPH Patient Survey Other Issues Related to Marijuana Use by Age Group (Among the 5433 Respondents who have Used Medical Use of Marijuana or Marijuana Products for at least 6 Months)

	Total N %	Age Group		
		≤ 50 years (N=3584)	≥ 51 years (N=3188)	p-value
Treated in an emergency room or urgent care facility for any reason related to marijuana or marijuana product use?	6499			ns
0 times	6492 99.89	3363 99.88	3016 99.90	
At least once	7 0.11	4 0.12	3 0.10	
In the past 12 months, have you needed to consume larger amounts of marijuana or marijuana products in order to feel the same effects?	5011			****
No	4313 86.07	2097 81.09	2141 91.65	
Yes	698 13.93	489 18.91	195 8.35	
In the past 12 months, have you tried to cut down on your marijuana or marijuana product use?	5010			****
No	4094 81.72	1990 77.04	2030 86.83	
Yes	916 18.28	593 22.96	308 13.17	
In the past 12 months, have you felt sick or had withdrawal symptoms because you stopped or cut down on your marijuana or marijuana product use? †	863			ns
No	786 91.08	499 89.75	270 93.10	
Yes	77 8.92	57 10.25	20 6.90	
† Among respondents who reported trying to cut down on marijuana or marijuana product use in the past 12 months *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 18C: DPH Patient Survey Other Issues Related to Marijuana Use by Education (Among All 6,934 Respondents)

	Total N %	Education		
		< Bachelor's (N=3282)	≥ Bachelor's (N=3595)	p-value
Have you noticed any of the following <i>negative</i> outcomes/consequences related to your marijuana use?	6572			
Negative changes in mood or mental health	141 2.15	65 2.08	75 2.18	ns
Reduction in physical health	57 0.87	28 0.90	29 0.84	ns
Negative changes in cognition	435 6.62	163 5.23	271 7.89	****
Negative changes in social relationships	75 1.14	38 1.22	37 1.08	ns
Occupation/job-related issues	58 0.88	38 1.22	19 0.55	**
Other outcomes/consequences	370 5.63	143 4.58	226 6.58	***
No negative outcomes/consequences	5452 82.96	2640 84.64	2799 81.51	***
Have you noticed any of the following <i>positive</i> outcomes/consequences related to your marijuana use?	6572			
Positive changes in mood or mental health	5158 78.48	2488 79.77	2656 77.34	*
Improved physical health	4435 67.48	2180 69.89	2246 65.40	***
Positive changes in cognition	1979 30.11	1101 35.30	872 25.39	****
Positive changes in social relationships	2717 41.34	1420 45.53	1290 37.57	****
Other outcomes/consequences	1005 15.29	430 13.79	567 16.51	**
No positive outcomes/consequences	168 2.56	78 2.50	90 2.62	ns

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$; ns=not significant

Table 18C: DPH Patient Survey Other Issues Related to Marijuana Use by Education (Among the 5433 Respondents who have Used Medical Use of Marijuana or Marijuana Products for at least 6 Months)

	Total N %	Education		
		< Bachelor's (N=3282)	≥ Bachelor's (N=3595)	p-value
Treated in an emergency room or urgent care facility for any reason related to marijuana or marijuana product use?	6499			**
0 times	6492 99.89	3077 99.77	3399 100.00	
At least once	7 0.11	7 0.23	0 0.00	
In the past 12 months, have you needed to consume larger amounts of marijuana or marijuana products in order to feel the same effects?	5011			ns
No	4313 86.07	2065 85.12	2240 86.96	
Yes	698 13.93	361 14.88	336 13.04	
In the past 12 months, have you tried to cut down on your marijuana or marijuana product use?	5010			*
No	4094 81.72	1930 80.32	2156 82.99	
Yes	916 18.28	473 19.68	442 17.01	
In the past 12 months, have you felt sick or had withdrawal symptoms because you stopped or cut down on your marijuana or marijuana product use? †	863			ns
No	786 91.08	406 90.83	377 91.28	
Yes	77 8.92	41 9.17	36 8.72	

† Among respondents who reported trying to cut down on marijuana or marijuana product use in the past 12 months

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

Alcohol Consumption

All respondents were asked to report on their alcohol consumption in the past 30 days and other related behaviors. Results are summarized in *Tables 19A, 19B, and 19C*, with comparisons by gender, age group, and educational attainment, respectively.

Forty-one percent of survey respondents reported no days in the past 30 days in which they consumed an alcoholic beverage, 42% reported consuming alcohol between 1 and 10 days, and 17% reported consuming alcohol more than 10 days in the past 30. A larger proportion of respondents over the age of 50 than younger respondents reported consuming no alcoholic beverages in the past 30 days (43% vs. 39%) and consuming alcohol for at least 21 days out of the past 30 (10% vs. 4%). A larger proportion of respondents under the age of 51 than older respondents reported consuming an alcoholic beverage between 1 and 10 days out of the past 30 (47% vs. 36%). A larger proportion of respondents without a Bachelor's degree than respondents with a degree reported consuming no alcoholic beverages in the past 30 days (53% vs. 31%), while a larger proportion of respondents with a Bachelor's degree than respondents without a degree reported consuming an alcoholic beverage between 1 and 10 days out of the past 30 (47% vs. 36%), between 11 and 20 days out of the past 30 (14% vs. 6%), and over 21 days out of the past 30 (8% vs. 5%).

Fifty-one percent of survey respondents reported spending \$0 on alcohol in the past 30 days, 42% of respondents reported spending between \$1 and \$100, and 6% reported spending more than \$100. A larger proportion of females than males reported spending \$0 (54% vs. 49%), and a larger proportion of males than females reported spending more than \$100 (8% vs. 4%). A larger proportion of respondents over the age of 51 than under reported spending \$0 on alcohol in the last 30 days (54% vs. 48%), while a larger proportion of younger respondents reported spending between \$1 and \$100 (44% vs. 41%). A larger proportion of respondents without a Bachelor's degree than with a degree reported spending \$0 on alcohol in the past 30 days (63% vs. 41%), while a larger proportion of respondents with a degree reported spending between \$1 and \$100 (50% vs. 35%), between \$101 and \$200 (7% vs. 2%) and over \$200 (3% vs. 1%).

Ninety-four percent of respondents who reported having at least one alcoholic beverage in the past 30 days reported that they did not drive while under the influence of alcohol in the last 30 days, while 6% reported that they had. There were no significant differences in the proportion of respondents driving under the influence of alcohol by gender, age, or education. 7% of survey respondents reported riding as a passenger in a vehicle while the driver was under the influence in the past 30 days.

Only 0.1% of survey respondents indicated being treated in an emergency room or urgent care facility for reasons related to alcohol use in the past 30 days. There were no significant differences in the proportion of respondents treated in an emergency room or urgent care facility for any reason related to alcohol use by gender, age, or education.

Table 19A: DPH Patient Survey Alcohol Consumption by Gender (Among All 6,934 Respondents)

	Total N %	Gender		
		Male (N=3732)	Female (N=3056)	p-value
Number of days respondent consumed an alcoholic beverage in past 30 days	6252			***
0 days	2569 41.09	1376 41.15	1146 40.84	
1-10 days	2609 41.73	1337 39.98	1233 43.94	
11-20 days	656 10.49	389 11.63	253 9.02	
21-30 days	418 6.69	242 7.24	174 6.20	
Money spent on alcohol in past 30 days	5328			****
\$0	2727 51.18	1409 48.86	1267 53.71	
\$1 to \$100	2260 42.42	1234 42.79	996 42.22	
\$101 to \$200	240 4.50	167 5.79	70 2.97	
\$201 or more	101 1.90	74 2.57	26 1.10	
<u>Drove/operated motor vehicle while under the influence of alcohol †</u>	3211			ns
No	3016 93.93	1579 93.32	1392 94.76	
Yes	182 5.67	104 6.15	73 4.97	
Don't know/not sure	13 0.40	9 0.53	4 0.27	
<u>Rode as a passenger in motor vehicle when driver under influence of alcohol</u>	6343			**
No	5901 93.03	3188 93.85	2621 92.03	
Yes	442 6.97	209 6.15	227 7.97	
<u>Treated in emergency room for any reason related to alcohol use</u>	6461			ns
No	6454 99.89	3459 99.86	2890 99.93	
Yes	7 0.11	5 0.14	2 0.07	

† Among respondents indicating consuming at least one drink of any alcoholic beverage in the past 30 days
 *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

Table 19B: DPH Patient Survey Alcohol Consumption by Age Group (Among All 6,934 Respondents)

	Total N %	Age Group		
		≤ 50 years (N=3584)	≥ 51 years (N=3188)	p-value
Number of days respondent consumed an alcoholic beverage in past 30 days	6252			****
0 days	2569 41.09	1267 39.19	1251 42.97	
1-10 days	2609 41.73	1509 46.67	1056 36.28	
11-20 days	656 10.49	332 10.27	318 10.92	
21-30 days	418 6.69	125 3.87	286 9.82	
Money spent on alcohol in past 30 days	5328			****
\$0	2727 51.18	1338 48.44	1334 53.79	
\$1 to \$100	2260 42.42	1206 43.66	1024 41.29	
\$101 to \$200	240 4.50	150 5.43	89 3.59	
\$201 or more	101 1.90	68 2.46	33 1.33	
Drove/operated motor vehicle while under the influence of alcohol †	3211			ns
No	3016 93.93	1703 94.04	1265 93.70	
Yes	182 5.67	98 5.41	82 6.07	
Don't know/not sure	13 0.40	10 0.55	3 0.22	
Rode as a passenger in motor vehicle when driver under influence of alcohol	6343			*
No	5901 93.03	3030 92.24	2767 93.86	
Yes	442 6.97	255 7.76	181 6.14	
Treated in emergency room for any reason related to alcohol use	6461			ns
No	6454 99.89	3345 99.85	2996 99.93	
Yes	7 0.11	5 0.15	2 0.07	

† Among respondents indicating consuming at least one drink of any alcoholic beverage in the past 30 days

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant

Table 19C: DPH Patient Survey Alcohol Consumption by Education (Among All 6,934 Respondents)

	Total N %	Education		
		< Bachelor's (N=3282)	≥ Bachelor's (N=3595)	p-value
Number of days respondent consumed an alcoholic beverage in past 30 days	6252			****
0 days	2569 41.09	1555 52.78	1007 30.59	
1-10 days	2609 41.73	1066 36.18	1537 46.69	
11-20 days	656 10.49	187 6.35	469 14.25	
21-30 days	418 6.69	138 4.68	279 8.48	
Money spent on alcohol in past 30 days	5328			****
\$0	2727 51.18	1604 62.51	1114 40.51	
\$1 to \$100	2260 42.42	889 34.65	1369 49.78	
\$101 to \$200	240 4.50	45 1.75	194 7.05	
\$201 or more	101 1.90	28 1.09	73 2.65	
<u>Drove/operated motor vehicle while under the influence of alcohol †</u>	3211			ns
No	3016 93.93	1160 94.16	1851 93.77	
Yes	182 5.67	66 5.36	116 5.88	
Don't know/not sure	13 0.40	6 0.49	7 0.35	
<u>Rode as a passenger in motor vehicle when driver under influence of alcohol</u>	6343			**
No	5901 93.03	2853 94.10	3034 92.02	
Yes	442 6.97	179 5.90	263 7.98	
<u>Treated in emergency room for any reason related to alcohol use</u>	6461			ns
No	6454 99.89	3062 99.87	3377 99.91	
Yes	7 0.11	4 0.13	3 0.09	
† Among respondents indicating consuming at least one drink of any alcoholic beverage in the past 30 days *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Non-Medical Use of Prescription Drugs and Other Substances

All respondents were asked to report on their non-medical use or and behaviors related to prescription drugs and other substances in the past 30 days. Results are summarized

in *Tables 20A, 20B, and 20C*, with comparisons by gender, age group, and educational attainment, respectively.

Ninety percent of survey respondents reported no use of cocaine or crack, heroin, anxiety drugs, sleeping drugs, prescription opioids, or other drugs for non-medical purposes in the past 30 days. 3% of respondents reported using anxiety drugs such as sedatives, tranquilizers, and anxiolytics, and 2% reported using sleeping drugs such as benzodiazepines and barbiturates in the past 30 days. Less than 2% reported using prescription opioids such as Oxycodone, OxyContin, Hydrocodone, Vicodin, Morphine, Methadone, or Fentanyl in the past 30 days. Less than 1% reported using cocaine, crack, or heroin in the past 30 days.

Thirty-five percent of respondents who reported any use of cocaine or crack, heroin, anxiety drugs, sleeping drugs, prescription opioids, or other drugs for non-medical purposes in the past 30 days reported non-medical use of prescription drugs between 1 and 10 days out of the past 30, while 65% reported non-medical use of prescription drugs and other substances for more than 10 out of 30 days.

One percent of respondents who reported any use of cocaine or crack, heroin, anxiety drugs, sleeping drugs, prescription opioids, or other drugs for non-medical purposes in the past 30 days being treated in an emergency room or urgent care facility for reasons related to non-medical use of prescription drugs and other substances in the past 30 days. There were no significant differences in the proportion of respondents treated in emergency rooms for non-medical use of prescription drugs or other substances in the past 30 days by gender, age, or education.

Fifty-nine percent of survey respondents reported cutting down or stopping the use of other prescription drugs, over the counter medications, or other substances since beginning marijuana use. A significantly larger proportion of female respondents compared to male (63% vs. 55%).

Sixty percent of survey respondents reported spending \$0 on prescription drugs or other substances, and 31% of respondents reported spending between \$1 and \$100, and 9% reported spending over \$100 in the past 30 days. A larger proportion of male respondents than female reported spending \$0 on any other prescription drugs (63% vs. 57%), while a larger proportion of female respondents than male reported spending between \$1 and \$100 on any other prescription drugs (34% vs. 28%) in the past 30 days. A larger proportion of respondents under age 51 than over reported spending \$0 on any other prescription drugs (67% vs. 53%), while a larger proportion of older respondents than younger reported spending between \$1 and \$100 on any other prescription drugs in the past 30 days (36% vs. 25%). A larger proportion of respondents without a Bachelor's degree than respondents with a degree reported spending \$0 on any other prescription drugs in the past 30 days (65% vs. 56%), while a larger percent of respondents with a Bachelor's degree than without reported spending between \$1 and \$100 (34% vs. 27%).

Four percent of respondents who indicated using prescription drugs or other substances for non-medical purposes in the past 30 days reported operating a vehicle while under the influence or prescription or other drugs in the past 30 days. 2% of survey respondents reported riding as a passenger in a vehicle while the driver was under the influence or prescription or other drugs in the past 30 days.

Table 20A: DPH Patient Survey Non-Medical Use of Prescription Drugs and Other Substances by Gender (Among All 6,934 Respondents)

	Total N %	Gender		
		Male (N=3732)	Female (N=3056)	p-value
Used any of the following drugs for non-medical purposes †	6435			
None	5852 90.07	3175 90.92	2585 89.20	*
Cocaine or Crack	16 0.25	9 0.26	7 0.24	ns
Heroin	2 0.03	1 0.03	1 0.03	ns
Antianxiety drugs (sedatives, Tranquilizers, Anxiolytics)	185 2.85	84 2.41	99 3.42	*
Sleeping drugs (Benzodiazepines, Barbiturates)	145 2.23	69 1.98	74 2.55	ns
Prescription opioids (Oxycodone/ OxyContin, Hydrocodone/ Vicodin, Morphine, Methadone, Fentanyl)	123 1.89	66 1.89	53 1.83	ns
Other	112 1.72	53 1.52	56 1.93	ns
Number of days respondent used any of the above drugs in past 30 days	351			ns
1-10 days	124 35.33	56 34.36	66 36.46	
More than 10 days	227 64.67	107 65.64	115 63.54	
Treated in an emergency room for any reason related to use of any of the above drug(s) ‡	462			ns
No	457 98.92	217 98.64	234 99.57	
Yes	5 1.08	3 1.36	1 0.43	
† Percentages sum to more than 100% because respondents could choose more than one option ‡ Among respondents indicating USING cocaine or crack, heroin, antianxiety, sleeping, or prescription opioids for non-medical purposes in the past 30 days *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

(Continued) Table 20A: DPH Patient Survey Non-Medical Use of Prescription Drugs and Other Substances by Gender (Among All 6,934 Respondents)

	Total N %	Gender		
		Male (N=3732)	Female (N=3056)	p-value
Since beginning to use marijuana, respondent cut down or stopped using any other prescription drugs, over the counter medications, or other substance	6010			****
No	2475 41.18	1433 44.67	1006 37.12	
Yes	3535 58.82	1775 55.33	1704 62.88	
Total money spent on drugs (prescription or other substances) in past 30 days	4762			****
\$0	2870 60.27	1598 62.72	1228 57.28	
\$1 to \$100	1453 30.51	704 27.63	729 34.00	
\$101 to \$200	184 3.86	111 4.36	70 3.26	
\$201 or more	255 5.35	135 5.30	117 5.46	
Drove /operated motor vehicle when under the influence (medical prescription drugs only) †	5746			ns
No	5436 94.60	2943 94.63	2407 94.50	
Yes	205 3.57	107 3.44	98 3.85	
Don't know/not sure	105 1.83	60 1.93	42 1.65	
Rode as a passenger in motor vehicle when under the influence of any of the above drugs	6175			ns
No	6031 97.67	3247 97.83	2696 97.47	
Yes	144 2.33	72 2.17	70 2.53	
† Among respondents indicating NOT using cocaine or crack, heroin, antianxiety, sleeping, or prescription opioids for non-medical purposes in the past 30 days *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 20B: DPH Patient Survey Non-Medical Use of Prescription Drugs and Other Substances by Age Group (Among All 6,934 Respondents)

	Total N %	Age Group		
		≤ 50 years (N=3584)	≥ 51 years (N=3188)	p-value
Used any of the following drugs for non-medical purposes †	6435			
None	5852 90.07	3080 91.31	2678 88.94	**
Cocaine or Crack	16 0.25	15 0.44	1 0.03	***
Heroin	2 0.03	1 0.03	1 0.03	ns
Antianxiety drugs (sedatives, Tranquilizers, Anxiolytics)	185 2.85	89 2.64	93 3.09	
Sleeping drugs (Benzodiazepines, Barbiturates)	145 2.23	61 1.81	81 2.69	*
Prescription opioids (Oxycodone/ OxyContin, Hydrocodone/ Vicodin, Morphine, Methadone, Fentanyl)	123 1.89	43 1.27	76 2.52	***
Other	112 1.72	46 1.36	65 2.16	*
Number of days respondent used any of the above drugs in past 30 days	351			*
1-10 days	124 35.33	62 41.89	60 30.30	
More than 10 days	227 64.67	86 58.11	138 69.70	
Treated in an emergency room for any reason related to use of any of the above drug(s) ‡	462			ns
No	457 98.92	191 97.95	257 99.61	
Yes	5 1.08	4 2.05	1 0.39	
† Percentages sum to more than 100% because respondents could choose more than one option ‡ Among respondents indicating USING cocaine or crack, heroin, antianxiety, sleeping, or prescription opioids for non-medical purposes in the past 30 days *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

(Continued) Table 20B: DPH Patient Survey Non-Medical Use of Prescription Drugs and Other Substances by Age Group (Among All 6,934 Respondents)

	Total N %	Age Group		
		≤ 50 years (N=3584)	≥ 51 years (N=3188)	p-value
Since beginning to use marijuana, respondent cut down or stopped using any other prescription drugs, over the counter medications, or other substance	6010			***
No	2475 41.18	1195 38.75	1224 43.37	
Yes	3535 58.82	1889 61.25	1598 56.63	
Total money spent on drugs (prescription or other substances) in past 30 days	4762			****
\$0	2870 60.27	1661 66.63	1161 53.04	
\$1 to \$100	1453 30.51	629 25.23	798 36.46	
\$101 to \$200	184 3.86	75 3.01	104 4.75	
\$201 or more	255 5.35	128 5.13	126 5.76	
Drove /operated motor vehicle when under the influence (medical prescription drugs only) †	5746			***
No	5436 94.60	2898 95.77	2449 93.19	
Yes	205 3.57	83 2.74	120 4.57	
Don't know/not sure	105 1.83	45 1.49	59 2.25	
Rode as a passenger in motor vehicle when under the influence of any of the above drugs	6175			ns
No	6031 97.67	3130 97.66	2800 97.77	
Yes	144 2.33	75 2.34	64 2.23	
† Among respondents indicating NOT using cocaine or crack, heroin, antianxiety, sleeping, or prescription opioids for non-medical purposes in the past 30 days *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 20C: DPH Patient Survey Non-Medical Use of Prescription Drugs and Other Substances by Education (Among All 6,934 Respondents)

	Total N %	Education		
		< Bachelor's (N=3282)	≥ Bachelor's (N=3595)	p-value
Used any of the following drugs for non-medical purposes †	6435			
None	5852 90.07	2754 89.53	3083 90.57	ns
Cocaine or Crack	16 0.25	10 0.33	6 0.18	ns
Heroin	2 0.03	2 0.07	0 0.00	ns
Antianxiety drugs (sedatives, Tranquilizers, Anxiolytics)	185 2.85	96 3.12	89 2.61	ns
Sleeping drugs (Benzodiazepines, Barbiturates)	145 2.23	64 2.08	81 2.38	ns
Prescription opioids (Oxycodone/ OxyContin, Hydrocodone/ Vicodin, Morphine, Methadone, Fentanyl)	123 1.89	79 2.57	44 1.29	***
Other	112 1.72	57 1.85	55 1.62	ns
Number of days respondent used any of the above drugs in past 30 days	351			ns
1-10 days	124 35.33	50 30.30	74 39.78	
More than 10 days	227 64.67	115 69.70	112 60.21	
Treated in an emergency room for any reason related to use of any of the above drug(s) ‡	462			ns
No	457 98.92	233 98.31	224 99.56	
Yes	5 1.08	4 1.69	1 0.44	
† Percentages sum to more than 100% because respondents could choose more than one option ‡ Among respondents indicating USING cocaine or crack, heroin, antianxiety, sleeping, or prescription opioids for non-medical purposes in the past 30 days *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

(Continued) Table 20C: DPH Patient Survey Non-Medical Use of Prescription Drugs and Other Substances by Education (Among All 6,934 Respondents)

	Total N %	Education		
		< Bachelor's (N=3282)	≥ Bachelor's (N=3595)	p-value
Since beginning to use marijuana, respondent cut down or stopped using any other prescription drugs, over the counter medications, or other substance	6010			ns
No	2475 41.18	1162 41.56	1309 40.92	
Yes	3535 58.82	1634 58.44	1890 59.08	
Total money spent on drugs (prescription or other substances) in past 30 days	4762			****
\$0	2870 60.27	1443 65.24	1421 55.90	
\$1 to \$100	1453 30.51	597 26.99	856 33.67	
\$101 to \$200	184 3.86	78 3.53	105 4.13	
\$201 or more	255 5.35	94 4.25	160 6.29	
Drove /operated motor vehicle when under the influence (medical prescription drugs only) †	5746			ns
No	5436 94.60	2556 94.32	2866 94.87	
Yes	205 3.57	100 3.69	105 3.48	
Don't know/not sure	105 1.83	54 1.99	50 1.66	
Rode as a passenger in motor vehicle when under the influence of any of the above drugs	6175			**
No	6031 97.67	2849 97.00	3169 98.26	
Yes	144 2.33	88 3.00	56 1.74	
† Among respondents indicating NOT using cocaine or crack, heroin, antianxiety, sleeping, or prescription opioids for non-medical purposes in the past 30 days *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Combination of Substances

All respondents were asked to report on their combination use of alcohol, marijuana, or other drugs in the past 30 days. Results are summarized in *Tables 21A, 21B, and 21C*, with comparisons by gender, age group, and educational attainment, respectively.

Thirty-seven percent of survey respondents reported using a combination of alcohol, marijuana, or other drugs in the past 30 days. A significantly larger proportion of respondents younger than 51 years old compared to older respondents reported combination use between 1 to 10 days out of the past 30 (25% vs. 19%), as did a significantly larger proportion of respondents with a Bachelor's degree compared to respondents without a degree (27% vs. 16%). A larger proportion of respondents older than 50 years old compared to younger respondents reported combination use for at least 11 days out of the past 30 (19% vs. 11%), as did a larger proportion of respondents with a Bachelor's degree compared to respondents without a degree (16% vs. 13%).

Nine percent of respondents who indicated using a combination of alcohol, marijuana, or other drugs in the past 30 days reported operating a vehicle while under the influence of combination substances in the past 30 days. There were no significant differences in the proportion of respondents who reported driving/operating a car or other motor vehicle under the influence of any combination of alcohol, marijuana, or other drugs by gender, age, or education.

Table 21A: DPH Patient Survey Combination of Substances by Gender (Among All 6,934 Respondents)

	Total N %	Age Group		
		≤ 50 years (N=3584)	≥ 51 years (N=3188)	p-value
Number of days respondent used a combination of alcohol, marijuana, or other drugs (prescription drugs or other substances) in past 30 days	5947			****
None	3772 63.43	1989 64.12	1714 62.28	
1-10 days	1321 22.21	782 25.21	521 18.93	
More than 10 days	854 14.36	331 10.67	517 18.79	
<u>Drove/operated</u> a motor vehicle when under the influence of any combination of alcohol, marijuana, or other drugs †	2109			ns
No	1918 90.94	975 90.28	920 91.45	
Yes	191 9.06	105 9.72	86 8.55	
† Among respondents indicating use of a combination of alcohol, marijuana, or other drugs in the past 30 days *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

**Table 21B: DPH Patient Survey Combination of Substances by Age Group
(Among All 6,934 Respondents)**

	Total N %	Age Group		
		≤ 50 years (N=3584)	≥ 51 years (N=3188)	p-value
Number of days respondent used a combination of alcohol, marijuana, or other drugs (prescription drugs or other substances) in past 30 days	5947			****
None	3772 63.43	1989 64.12	1714 62.28	
1-10 days	1321 22.21	782 25.21	521 18.93	
More than 10 days	854 14.36	331 10.67	517 18.79	
<u>Drove/operated</u> a motor vehicle when under the influence of any combination of alcohol, marijuana, or other drugs †	2109			ns
No	1918 90.94	975 90.28	920 91.45	
Yes	191 9.06	105 9.72	86 8.55	
† Among respondents indicating use of a combination of alcohol, marijuana, or other drugs in the past 30 days *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Table 21C: DPH Patient Survey Combination of Substances by Education (Among All 6,934 Respondents)

	Total N %	Education		
		< Bachelor's (N=3282)	≥ Bachelor's (N=3595)	p-value
Number of days respondent used a combination of alcohol, marijuana, or other drugs (prescription drugs or other substances) in past 30 days	5947			****
None	3772 63.43	1995 71.00	1770 56.64	
1-10 days	1321 22.21	463 16.48	854 27.33	
More than 10 days	854 14.36	352 12.53	501 16.03	
<u>Drove/operated</u> a motor vehicle when under the influence of any combination of alcohol, marijuana, or other drugs †	2109			ns
No	1918 90.94	724 91.88	1189 90.35	
Yes	191 9.06	64 8.12	127 9.65	
† Among respondents indicating use of a combination of alcohol, marijuana, or other drugs in the past 30 days *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; ns=not significant				

Discussion

There were no notable differences between respondent distributions of gender, age, or county of residence groups comparing all respondents of the 2018 Medical Use of Marijuana Patient Survey to the full eligible population, suggesting that, although the response rates was low at 16%, the sample of 6934 respondents in this study was representative of the Massachusetts Medical Use of Marijuana patient population. In this survey respondents were asked to type in their Medical Marijuana Registration number and that may have led to concerns about confidentiality.

Respondents indicated using marijuana for an average of 23.5 days out of the past 30, with over 60% reporting marijuana use at least 21 out of the past 30. Over 90% of respondents indicated some certified medical use of marijuana, 6% some uncertified medical use, and 17% indicated some recreational use. These categories are not mutually exclusive, suggesting that while most respondents are using marijuana to treat medical conditions, but some are also using recreationally.

Results from this survey suggest that respondents appear to be treating a wide range of medical conditions, and often more than one at a time. The top 5 medical conditions being treated were anxiety (60% or all respondents), chronic pain (46%), insomnia (43%), depression (42%), and stress (41%), and the average number of conditions being treated by medical marijuana is 4.7.

Patients registered with the Massachusetts Department of Public Health Medical Use of Marijuana Program were certified by a qualified physician or clinician because of a debilitating medical situation, which often has multiple associated medical conditions for which marijuana use can assuage. Results from this study confirm this, suggesting that patients believe marijuana use is alleviating multiple.

While a qualified physician or clinician may certify a patient with a debilitating medical condition for medical use of marijuana, they are not required to write a prescription specifying the product type the patient must use (although they may make recommendations as the patient is under their care). As such, patients have access to a wide range of marijuana administration methods. Results from this study indicate that respondents use multiple methods of administration, over the course of 30 days, with an average of 2.9 methods. In fact, less than one fifth of all respondents reported only one method of marijuana administration, while over 30% reported using 4 or more. The most common method of marijuana administration was smoking dried flower (65%), followed by vaporized marijuana concentrate (62%) and edible marijuana products (51%).

All respondents were asked questions related to perceptions of the Medical Use of Marijuana Program. In general, respondents reported favorably towards medical use of marijuana. Almost all respondents considered the use to be effective in treating their conditions with over 65% of respondents reported that they believed use of marijuana or marijuana products has been “very effective” and an additional 26% believed use of marijuana to be “effective”. Also almost 90% of respondents reported that they had “somewhat high” or “very high” confidence that they were receiving safe, uncontaminated products when purchasing marijuana or marijuana products at a licensed dispensary. 94% reported feeling “somewhat safe” or “very safe” when purchasing medical marijuana at a licensed dispensary, and 66% reported “somewhat high” or “very high” knowledge of their recommended marijuana or marijuana product based on the information provided by their certified practitioner. Findings from this study also suggest that respondents perceive marijuana use to have very high rates of positive outcomes and little obvious harm. 78% of respondents reported positive changes in their mood or mental health, 67% reported improved physical health, and 83% reported no negative outcomes or consequences related to their marijuana use. Thus, respondents are highly satisfied with their access to marijuana products and information and believe they have largely benefitted from medical use of marijuana with very little, if any negative effects.

Finally, almost 60% of respondents who reported use of prescription drugs, over-the-counter, medications, or other substances (for medical use only) also reported cutting down or stopping use of other prescription drugs, over the counter medications, or other substances since beginning to use marijuana.

Conclusion/Public Health Implications

The Massachusetts Medical Marijuana Program is considered to be a very important and valuable asset to the mental and physical health of participants. Respondents of the 2018 Medical Use of Marijuana Patient Survey indicate general satisfaction with the program, few negative outcomes, and in particular have reported a reduction in the use of other drugs and medications as a result of marijuana use.

Task 2: Incidents of Impairment and Hospitalization

Chapter 1: Measuring Marijuana Exposure and its Effects Related to Driving Impairment: A State of the Science Review

Introduction

In states that have chosen to legalize marijuana, one concern among public health and public safety professionals and citizens is the potential impact of marijuana legalization on motor vehicle crashes (MVCs). Studies suggest that recent cannabis use is associated with an increased crash risk between 22%-100% (Asbridge, Hayden, & Cartwright, 2012; G. Li, Chihuri, & Brady, 2017; Rogeberg & Elvik, 2016). However, there are challenges to the detection and deterrence of marijuana-impaired driving. Although a substantial body of literature related to methods for identifying acute marijuana exposure and impairment exists, best practice for doing so has yet to be established. As such, states that are implementing legalization of marijuana are doing so without established guidelines for detecting marijuana-impaired driving in a manner that is relatively non-invasive and sufficiently accurate to prove impairment. Washington State has selected 5ng/mL as a per se limit; Colorado uses this level as “presumptive evidence” of impairment. This report reviews the relevant scientific literature on the topic of measuring marijuana as it relates to driving impairment.

Scientific Foundation

The content of this report is predicated on several accepted premises that are derived from current scientific knowledge. First, with regard to marijuana pharmacokinetics, it is established that combustion (burning) of the dried flower of the cannabis plant converts tetrahydrocannabinolic acid to Δ^9 -tetrahydrocannabinol (THC) (Huestis, 2007). THC is then metabolized in the liver to psychoactive 11-OH- Δ^9 -tetrahydrocannabinol (OH-THC; pronounced “hydroxy THC”) and non-psychoactive 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol (THC-COOH, pronounced “carboxy THC”) which is excreted in urine (Grotenhermen, 2003; Huestis, 2007).

The Δ^9 -THC is the main source of the pharmacological effects caused by cannabis consumption. Cannabinoids exert many effects through activation of G-protein-coupled cannabinoid receptors in the brain and peripheral tissues (Grotenhermen, 2003). There is also evidence for non-receptor-dependent mechanisms (Grotenhermen, 2003). Cannabis is usually inhaled or taken orally. The pharmacokinetics of THC vary by route of administration (Grotenhermen, 2003; Huestis, 2007; Newmeyer et al., 2017a). After inhalation, plasma THC concentration peak within a few minutes (Grotenhermen, 2003). Psychotropic effects begin within seconds to a few minutes, reach a maximum after 15-30 minutes, and taper off within 2-3 hours (Grotenhermen, 2003). Following oral ingestion, psychotropic effects onset after 30-90 minutes, reach a maximum after 2-3 hours, and last for about 4-12 hours, depending on dose and specific effect (Grotenhermen, 2003; Hollister et al., 1981; Wall, Sadler, Brine, Taylor, & Perez-Reyes, 1983).

With regard to biological measurement of marijuana exposure, we take blood to be the “gold standard” in terms of the matrix that has been best studied. Urine and oral fluid have also been studied to a great extent. The relationship between route of administration and measurement of cannabis in oral fluid is an area of ongoing research and will be described below.

Prevalence of Cannabis-Positive Drivers in Motor Vehicle Crashes

In the U.S. estimates of the prevalence of marijuana involvement in MVCs vary. As part of the background information for this state of the science review (SSR) we systematically collected all studies reporting prevalence of cannabis involvement in MVCs in the U.S. At the national level, one study found that the prevalence of cannabis-involved motor vehicle crashes in 1982 was 10% and that by 2001, the prevalence had increased to 19.6% (Macdonald et al., 2003). Conversely, another nationwide study found that the overall prevalence of cannabis in motor vehicle crashes between the years 1993-2014 remained constant at 10.4% which suggests that prevalence had not increased significantly since 1982 (G. Li et al., 2017).

Studies have also been conducted at the state level in locations that have made substantial changes to their marijuana policy by allowing the legal sale of marijuana for medical and/or recreational purposes. States that have undergone such policy changes provide insight that may be especially relevant for Massachusetts. In Colorado, one study conducted between the years 1994-2011 found that there was an increase in prevalence of cannabis related motor vehicle crashes from 4.5% in 1994 to 10% in 2011, after medical marijuana was commercialized in mid-2009 (Salomonsen-Sautel, Min, Sakai, Thurstone, & Hopfer, 2014). Findings from another study in Colorado show that in 2006 the prevalence of cannabis related motor vehicle crashes in Colorado was 6.9% and increased to 19% by 2014; Colorado's citizens voted in 2012 to legalize marijuana for non-medical use (Rocky Mountain High Intensity Drug Trafficking Area, 2015).

Results from studies in Washington State indicate that about 10% of drivers in fatal crashes between 2010-2014 had delta-9-THC in their blood. The prevalence such crashes was stable prior to legalization of recreational marijuana use, but approximately 9 months after legalization took effect it began increasing by nearly 10 percentage points per year (Tefft, Arnold, & Grabowski, 2016). Another study from 2013-2014 showed the prevalence of cannabis related motor vehicle crashes in Washington State to be between 7-8% (Banta-Green, Rowhani-Rahbar, Ebel, Andris, & Qiu, 2016). Overall, there is conflicting evidence, but studies reviewed here indicate that the prevalence of cannabis-positive drivers in motor vehicle crashes has increased in states where marijuana policy has become more permissive. It is important to note that in these prevalence studies, whether drivers were actually impaired by cannabis at the time of the crash was not determined. Collecting a blood test from surviving drivers presents a challenge due to the invasive nature of blood collection; time delays between a crash and blood testing are common and problematic since delta-9-THC levels rapidly decrease after smoking (Wood, Brooks-Russell, & Drum, 2016).

Study Purpose

The establishment of fair and appropriate methods to detect marijuana-related driving impairment could help ensure public safety in environments with legal marijuana and

provide important information about prevalence. This review of the literature is undertaken for the purpose of summarizing the available scientific evidence. Specifically, we sought to: 1) Describe the analytical methods used to quantify marijuana exposure in laboratory and field settings; 2) Describe measurements of marijuana-related impairment that are relevant to operating a motor vehicle; and 3) Provide an integration and discussion of evidence for approaches that link marijuana-related measurements of exposure with measurements of impairment that are relevant to operating a motor vehicle.

Research Questions

RQ1: What is the most current science on quantifying marijuana exposure in an analytical chemistry laboratory or clinical laboratory setting in different matrices (blood, oral fluid, urine) through quantitative measurement of marijuana and its metabolites?

RQ2: What methods (e.g., devices, tests, kits, etc.) are currently available for quantifying marijuana exposure in the field and what is the precision and accuracy of these methods for detecting marijuana exposure (compared to laboratory-based methods)?

RQ3a: What are the cognitive and behavioral indicators of marijuana exposure that are relevant to operating a motor vehicle? How have these been characterized at baseline (non-impaired) levels?

RQ3b: How are the cognitive and behavioral effects of marijuana impairment measured in laboratory settings and in field settings? What validation has been conducted? What is the level of accuracy for determining impairment/non-impairment?

Methods

We approached the research questions above through a systematic literature search process. In instances when a high-quality review article was already published on the topic of interest, we used the review as a starting point and extracted information from the studies gathered by the review authors. We then conducted a search that covered the time period between the publication of the latest paper included in the review and December 2017. We conducted the searches in the following order: RQ2, RQ3a, RQ3b, RQ1. More information is provided below, and details of the search terms are provided in

Table 1. Search Strings.

Research Question 1: Quantifying Marijuana Exposure in a Laboratory Setting

Our systematic search conducted for R2 identified studies that were relevant to research question 1. Specifically, all identified R2 studies utilized similar confirmatory laboratory testing methods to identify marijuana exposure in blood, urine, and or saliva.

Given the consistency in the studies identified in R2, we were confident in our assessment that said methods were the state of the science. As such, the goal of our research specific to R1 was to identify one or more studies that confirmed our assessment. We did not deem a systematic review of the literature necessary to accomplish this goal. Instead, we developed several search strings to identify studies that provided an overview of current methods as well as potential future directions for laboratory marijuana exposure quantification, particularly in regards to new quantification and interpretation methods for THC metabolites.

We tested both complex and simple search strings to accomplish this goal. All search strings were tested on PubMed. We found that one particular simple search string performed best. The string identified 22 total references. Titles and abstracts were reviewed for relevance and a recent article written by a leading expert in the field was identified. Given that the content of this article matched closely to what we were attempting to procure, we chose to utilize it as the center piece of our response to this question. Other identified references, either from the broad R1 search or the systematic, targeted R2 search were utilized as appropriate.

Research Question 2: Methods for Quantifying Marijuana Exposure in a Field Setting

We conducted a systematic search of the current literature related to on-site testing devices, sometimes called point-of-collection tests (POCT), for measuring marijuana. We did not restrict the search to specific biological matrices (i.e. only blood, only oral fluid). We conducted our search in both PubMed and Web of Science, and searched the relevant gray literature (e.g. AAA Foundation, National Highway Transportation Safety Administration, etc.) for relevant studies. The search was limited to studies published in or after 1995.

Search strings were developed in consultation with a University of Massachusetts Amherst librarian with expertise in health science search string development. Searches were conducted on each separate database and abstracts were screened for appropriateness. To be considered for full text review, abstracts had to convey that the study met the following criteria: (1) was published in English, (2) was conducted in humans, (3) examined field devices or kits, and (4) examined marijuana exposure.

Studies identified as candidates for inclusion after the abstract screening process subsequently had their full text reviewed for appropriateness. After full text review, studies were excluded if: (1) Device assessed was only for collection and storage of sample; (2) Study did not assess devices capability as a rapid on-site test; (3) Study assessed devices used to measure synthetic cannabinoids; (4) Device assessed was a laboratory device (5) Study did not assess any on-site device; (6) Study did not provide sensitivity or specificity measurements of THC for tested device, or (7) Text of study was not in English.

Of 154 combined peer reviewed results identified through our initial searches, 84 were selected for full text review. A majority (61%) of these studies were obtained through PubMed. We identified one study from the gray literature for full text review.

During full text review, we identified a systematic review and meta-analysis conducted on our topic of interest in 2017 (latest year of included studies was 2015). We used this study as the centerpiece of our review and subsequently reviewed identified studies from 2015-2017 to update and supplement this already completed review. We identified 6 studies that were published beyond the 2015 review. Thus, these 7 studies form the basis of our review for this question. We reviewed the reference list of the 6 more recent, original studies and cross-checked this with the review article to ensure that all important papers relevant to the topic were included either in the existing review article or in the original research studies we identified and included.

We extracted information about sensitivity and specificity of the POCT devices as compared to laboratory methods, and we report accuracy when possible. Sensitivity refers to the percentage of cannabis-using individuals that were correctly identified as positive for cannabis. Specificity refers to the percentage of individuals who did not use cannabis that were correctly identified as non-users by a negative test result.

Given the complexity of the studies in this area, we summarized the results in several tables. In synthesizing and interpreting the studies, as a whole, we weighted studies with a larger sample size, controlled laboratory conditions, and comparisons between multiple devices as more salient than others.

Research Question 3A: Cognitive and Behavioral Effects Relevant to Driving

A systematic search of the current literature related to cognitive and behavioral indicators of marijuana exposure was conducted. Following advice from a health sciences librarian, we conducted our searches in both PubMed and Web of Science. We also sought input from the librarian for developing and refining our search string. Searches were conducted on each separate database and abstracts were screened for appropriateness. We did not limit the date range on this search.

Early in the review process, we identified a recent systematic review (Bondallaz et al., 2016) whose content matched closely with what we were attempting to procure. We judged this review to be of high quality, and therefore used it as the basis for our response to RQ3a. We extracted all individual studies from the review and reviewed them independently. We subsequently conducted an update search, using a search string developed in consultation with a health sciences librarian to identify any studies on the subject of interest published after 2013 (the newest study reviewed in the review article).

In total, 24 studies were extracted from the Bondallaz review. Our update search (2013-2017) initially yielded 367 results from PubMed and 316 from Web of Science. After abstract screening and removal of duplicates, we identified 15 studies for full text review from PubMed and 2 studies for full text review from Web of Science. After full text

review, we identified an additional 5 studies that had been published on the topic since the Bondallaz review for a total of 29 studies included in our review.

Detailed information such as THC dosage, user population, sample size, study setting, indicator tested, measurement approach, and results were extracted from studies included in final review. In order to standardize the information extraction, we defined the relevance of cognitive / behavioral indicators measured according to the recommended behavioral measurements outlined in Guidelines for Research on Drugged Driving (J Michael Walsh, Verstraete, Huestis, & Mørland, 2008). These include automotive behavior, control behavior, and executive planning. The only additional category defined outside of the three listed above was, “driving safety/performance metric.” This was only defined for driving simulator and on road studies which measured direct driving metrics such as mean speed and SD lateral position. This approach was adapted from the Bondallaz review which identified said behavioral measurements and grouped typical neurocognitive tests (Tower of London Task, Critical Tracking Task etc.) according to their corresponding behavioral measurement (Bondallaz et al. 2016 – Table 1) (Bondallaz et al., 2016). We expanded on this by incorporating these behavioral measurement categories into our analytic table.

After information from all studies was extracted to the large summary table, we further refined the analysis in order to enhance the digestibility of the results. We created four separate analytic tables grouped by study setting (lab, simulator, on road, and observational). Each table presents a refined analysis, where detailed results are omitted in favor of a simple summary of the results with regard to the impact of marijuana on task performance. We documented whether marijuana exposure hurt performance, improved performance, or had no effect on performance on specified tests. These tables are designed to allow the reader to digest the results at a higher level and examine trends otherwise invisible at increased levels of granularity.

Research Question 3B: Field Measurement of Marijuana’s Effects and Accuracy for Determining Impairment

The first component of research question 3b, which addresses how cognitive and behavioral effects of marijuana exposure are measured in a laboratory setting, was answered using the search results from research question 3a. Please refer to RQ3a methods for details on the search methods. Search efforts for this research question focused only on the latter part of the question, which attempts to determine how the cognitive behavioral impacts of marijuana exposure are measured in field settings and the validation and accuracy of those tools.

To accomplish this, four separate search strings / strategies were developed to answer this question (Table 1. Search Strings). PubMed was searched. The first string scanned the peer reviewed literature for studies of screening tools that measure cognitive/behavioral indicators of marijuana exposure. After abstract screening, this search did not return any results.

The second string searched the peer reviewed literature for studies of screening tools that measured indicators of cognitive / behavioral deficits. This was done to gain a broader understanding of currently available validated tools. The overall goal was to identify tools that may have utility when applied to measuring marijuana exposure. After abstract screening, this search returned 2 results.

The third string searched the peer reviewed literature for studies that assessed the validity of standardized field sobriety tests (SFSTs) for measuring marijuana. This search was conducted due to the fact that SFSTs are currently used by law enforcement to determine impairment. After abstract screening, this search returned 3 results.

The fourth component of this approach was to scan of the grey literature / internet for tools and or screening devices that might have utility in measuring cognitive or behavioral impacts of marijuana exposure. These included mobile applications. This search returned 5 results, but we excluded 2 apps that were designed generally for cognitive impairment but did not touch directly on tasks used to measure marijuana-related effects in laboratory settings. Results from the four searches were extracted into two separate analytic tables, one for peer reviewed results, and the other for non-peer reviewed results.

Table 1. Search Strings

Research Question	Database	Search String / Search Terms
RQ1	PubMed	Marijuana AND Biological Matrices
RQ2	PubMed	(((marijuana OR cannabis OR Cannabinoids OR Tetrahydrocannabinol OR THC) AND (On-site OR rapid OR field) AND (method OR test OR evaluation OR screening OR measurement OR "Point-of-Care Testing" AND (Device OR kit))))
RQ2	Web of Science	(((marijuana OR cannabis OR Cannabinoids OR Tetrahydrocannabinol OR THC) AND (On-site OR rapid) AND (test OR evaluation OR "screening" OR "measurement" OR "Point-of-Care Testing") AND (Device OR Kit))))
RQ2	NHTSA	Marijuana, Cannabis, Tetrahydrocannabinol. Cannabinoids, On site, Rapid, Test, Evaluation, Measurement, Device
RQ2	AAA Foundation	Marijuana, Cannabis, Tetrahydrocannabinol. Cannabinoids, On site, Rapid, Test, Evaluation, Measurement, Device
RQ3A	PubMed (Initial Search)	(cognitive OR cognition OR behavior) AND motor vehicle AND (operation OR driving OR drive)
RQ3A	Web of Science Initial Search	(cognitive OR cognition OR behavior) AND motor vehicle AND (operation OR driving OR drive)

RQ3A	PubMed (Update Search)	((neurocognitive OR neurocognition OR cognitive OR cognition OR Behavior OR Behavioral OR Performance)) AND ((driving OR drive)) AND ((marijuana OR cannabis OR Cannabinoids OR Tetrahydrocannabinol OR THC))
RQ3A	Web of Science (Update Search)	((neurocognitive OR neurocognition OR cognitive OR cognition OR Behavior OR Behavioral OR Performance)) AND ((driving OR drive)) AND ((marijuana OR cannabis OR Cannabinoids OR Tetrahydrocannabinol OR THC))
R3B	PubMed (Search String A)	(Cognitive OR Behavioral) AND (Marijuana OR Cannabis) AND (Field or On-site or road side) AND (Screening OR Test OR app OR measurement OR evaluation)
R3B	PubMed (Search String B)	(mobile) AND (Cognitive OR Behavioral) AND (Dysfunction OR Impairment) AND (app OR Test OR screening OR application OR evaluation OR measurement)
R3B	PubMed (Search String C)	(Marijuana OR Cannabis) AND (Impairment OR Effect OR Influence) AND (Standard Field Sobriety Test or SFST) AND (Accuracy OR Validity OR Effectiveness)
RQ3B	Google (Search D)	Mobile, app, test, screening, (name of specific test) Example: "mobile Stroop test"

Results

Research Question 1: Quantifying Marijuana Exposure in a Laboratory Setting

There are currently three widely accepted laboratory methods for measuring cannabinoids in human biological matrices: immunoassays, chromatography, and mass spectrometry (Huestis & Smith, 2018). Historically, Gas Chromatography with Mass Spectrometry (GC-MS) has been most frequently utilized method. However, recent desire to identify increasingly informative markers of marijuana exposure has led to more frequent utilization of liquid chromatography tandem mass spectrometry (LC-MS/MS) and high-resolution mass spectrometry (HR-MS) measurement methods. Among other advantages, the LC-MS/MS method allows simultaneous quantification of free and conjugated analytes in a single assay (Huestis & Smith, 2018). These methods also offer high sensitivity and specificity for detecting markers of cannabis use (Huestis & Smith, 2018).

LC-MS/MS and HR-MS methods are intriguing because they offer the ability to identify the Phase II THC metabolite (THC-Glucuronide) as well as cannabigerol (CBG), cannabinol (CBN), and tetrahydrocannabivarin (THCV) (Huestis & Smith, 2018). As research on marijuana metabolism continues to advance, particularly as it relates to quantifying exposure, identification of these metabolites becomes increasingly valuable. For instance, quantification of these metabolites can offer information that helps ascertain recent cannabis intake and or the transfer of cannabinoids to alternative matrices such as hair (Huestis & Smith, 2018).

The wide acceptance of these methods is apparent in examining confirmatory laboratory methods utilized in R2 studies. In 100% of the studies we identified in our systematic search of the literature for R2, at least one variation of these methods was used as the gold standard laboratory comparator for performance assessment of point of care detection devices. One recent systematic review related to POCT device assessment restricted their search to include only studies where some type of chromatographic assay was used as the confirmatory method (Scherer et al., 2017). Moreover, among the four most recently published independent studies assessing POCT devices against laboratory methods, 50% utilized the LC-MS/MS method (Edwards, Smith, & Savage, 2017; S. Gentili, Solimini, Tittarelli, Mannocchi, & Busardo, 2016; Newmeyer et al., 2017a; Swortwood et al., 2017). Coupled with the recent analysis from leading experts in quantitative cannabinoid measurement (Huestis & Smith, 2018) these results confirm that measurement of cannabinoids in human biological matrices (blood, oral fluid, and urine) using immunoassays, chromatography, and or mass spectrometry, particularly LC-MS/MS, is the current state of the science.

Research Question 2: Methods for Quantifying Marijuana Exposure in a Field Setting

Point-of-collection testing (POCT) devices make it possible to rapidly screen for cannabis exposure without the use of standard laboratory equipment. These devices typically test oral fluid or urine as these matrices are easier to obtain in a field setting than blood. Compared with urine analysis, oral fluid (OF) collection presents fewer concerns about privacy and adulterations. Drug testing in OF samples usually detects parent drugs, whereas testing of urine samples usually detects metabolites. This makes OF more reflective of recent drug use (Allen, 2011; Bosker & Huestis, 2009; Drummer, 2010; Scherer et al., 2017).

Our systematic search revealed one systematic review plus meta-analysis of 31 studies that was published in mid-2017 (Scherer et al, 2017). The papers that met inclusion criteria for this study were papers evaluating one or more POCT devices and using a validated chromatographic assay as the confirmatory method. Devices had to assess oral fluid as the biological matrix. Studies had to include analysis of cannabinoids as well as cocaine, amphetamines, benzodiazepines (BZD), and opioids. We extracted the results for cannabinoids alone from that publication for inclusion in this report. After exclusions, we also reviewed 6 original studies that were not already covered in the review article.

In the studies we included in this review, we found evidence for 16 POCT devices (i.e. tests, kits, etc.) that evaluate cannabis exposure in a field setting, with varying levels of evidence and validity testing. In their 2017 review, Scherer et al. noted that the most commonly evaluated devices were the Alere™ DDS2 (DDS2), the Dräger DrugTest 5000™ (DT5000), and the Drugwipe™ manufactured by Securetec. (Scherer et al., 2017) Across the studies we reviewed, the Alere™ DDS2 and the Dräger DrugTest 5000™ have the most research evidence available of the POCT devices described in the literature in terms of the number of studies, the number of participants in those studies, and the relevant variables included (i.e. frequent vs. chronic cannabis users,

route of cannabis exposure). These devices also performed well according to the Scherer review and thus are the focus of our description.

Our systematic search also returned one study comparing two urine tests (the EZCup and the Multi4Card) which we briefly describe below, though there was less evidence for these approaches to point-of-collection OF testing. We concur with the authors of prior studies who note that the ease of use of OF tests makes them a better candidate for field applications (M. A. Huestis et al., 2013).

Oral Fluid POCT Devices

In the Scherer review, the authors included studies that evaluated the following devices: Rapiscan™, OralLab™, SalivaScreen™, Toxiquik™, Oratect™, Uplink™, Drugwipe™, Dräger DrugTest 5000™, OraLine™, OralSTAT™, Impact™, Uplink™, RapidStat™, BIOSENS Dynamic™, DDS 806™, OrAlert™, and DDS™. The Drugwipe™ (Securetec, Germany) was the most commonly evaluated device among the studies (n = 17), followed by the DrugTest 5000™ (Dräger Safety AG & Co., Germany; n = 12), the Rapiscan™ (Cozart Biosciences Ltd., UK; n = 8) and the Rapid Stat™ (Mavand Solutions, Germany; n = 7) (Scherer et al., 2017). All other devices were evaluated in five or fewer studies. Most other articles we reviewed focused predominantly on the DT5000 or the Alere™ DDS2 (DDS2).

The Alere™ DDS2 is a battery operated handheld device that provides a rapid qualitative assessment (positive/negative) of the presence or absence of delta-9-THC in oral fluid above a concentration of 25ng/mL. Samples are collected using a swab cartridge. After collection, the cartridge is inserted into the device for analysis. Results are available in five minutes and the device does not require oversight while the analysis is taking place. The device features a simple user interface, is lightweight, and has the ability to store up to 10,000 unique samples in its memory at once ("Alere DDS@2 Mobile Test System: Rapid Screening for Drugs of Abuse in Oral Fluid," 2018).

The Dräger DrugTest 5000™ (DT5000) is a portable device that provides a rapid qualitative assessment (positive/negative) of the presence or absence of delta-9-THC above a concentration of 5ng/mL. Samples are collected using a test cassette. After collection, the cassette is inserted into the device for analysis. Results are available in less than 9 minutes in most cases and the device does not require oversight while the analysis is taking place. The device features a simple graphical display that communicates results in plain text and has the ability to store up to 500 results at one time. Stored results are tagged with date and time. Results can also be printed using the Dräger Mobile Printer ("Dräger DrugTest® 5000: Analysis system for detecting drugs," 2018).

Study Designs for Evaluating POCT Devices

A variety of study designs were included in the articles we reviewed. The review article by Scherer et al. included studies of oral fluid POCT drug tests among varied populations (e.g. drivers, drug users, laboratory participants, etc.). Generally speaking,

the methodology of the reviewed studies was a slight variation of the following: Participants ingested cannabis either by smoking, vaporizing, or consumption of foods such as brownies in a controlled environment. Upon cannabis consumption, oral fluid specimens were qualitatively analyzed (i.e. pass or fail) using the specified on-site device. Quantitative analytic specimens were concurrently collected to be used as comparators. Analytic samples were either blood or oral fluid (If oral fluid, usually collected with a Quantisal device) ("Quantisal™ Oral Fluid Collection Device," 2018) and were analyzed at a later date using standard, validated laboratory techniques. Results were obtained by comparing the performance of the on-site OF device to the validated laboratory method to determine sensitivity and specificity of the POC device. Most studies defined cut-off values for a "true positive" using only delta-9-THC, although one did conduct additional analyses that included combinations of delta-9-THC and other cannabinoids (we did not report on these results in our analysis). Of note, two studies did not administer cannabis in a controlled setting but rather screened for it in field settings (Edwards et al., 2017; S. Gentili et al., 2016). Otherwise, the general outline of their analyses were the same.

The choice of a confirmation cut-point matters for the correct identification of cannabis exposure via a POCT device. The European Union's Driving Under the Influence of Drugs, Alcohol, and Medicines (DRUID) program has suggested an 80% target for analytical sensitivity, specificity, and efficiency when evaluating devices (Blencowe, Pehrsson, & Lillsunde, 2010). The DRUID project utilized a confirmatory cutoff of 1ng/mL of delta-9-THC (Verstraete et al., 2011). The U.S. Substance Abuse and Mental Health Services Administration (SAMHSA) has recommended a cutoff of 2ng/mL as a definition for a positive cannabis test in a workplace setting (Department of Health and Human Services, 2015). Thus, the papers we reviewed most commonly report sensitivity and specificity at a variety of cutoffs: 25 ng/mL (the devices own cutoff for the DDS2), 5 ng/mL (the device cutoff for the DT5000), 2 ng/mL (SAMHSA), 1 ng/mL (DRUID), and 0.2 or 0.5 ng/mL (the limit of quantitation). Walsh's guidelines for research on drugged driving suggest that for drugs with therapeutic use, the confirmatory testing cut-off concentrations should be at least as low as the low end of the therapeutic range. For recreational drugs without any therapeutic use, the guidelines suggest use of a low analytical cut-off (J. M. Walsh, 2008; J Michael Walsh et al., 2008). For cannabis, which is used both medically and recreationally in Massachusetts, and has wide interpersonal variation in pharmacokinetics, establishing a cutoff presents a challenge. We, therefore, present sensitivity and specificity estimates at multiple cut-offs when possible.

Testing revealed, not unexpectedly, that sensitivity and specificity were highest when the cut-off level was highest (25ng/mL in the studies of OF POCT devices). The tests perform better at correctly identifying the presence of THC when higher levels of THC are present in the matrix. The 25ng/mL cutoff was assessed only for the DDS2 device, since this is the level above which it is designed to report a positive test.

Another important factor in examining the performance of POCTs is the cannabis use history of the study participants. Prior studies have documented that POCT device

sensitivity is higher in chronic frequent as compared to occasional cannabis smokers due to longer detection windows and higher true positive rates. (M. A. Huestis et al., 2013) Because THC is fat soluble, it is stored in adipose tissue and can leak back into circulation over time, even long after the psychoactive effects of acute cannabis use have ceased (Gunasekaran et al., 2009; Wong et al., 2014; Wong et al., 2013). However, at least one study has concluded that the cannabinoid concentration changes that result from THC reentering circulation are not likely to negatively impact the ability to correctly interpret a drug test (Westin, Mjønes, Burchardt, Fuskevåg, & Slørdal, 2014). In addition, since cannabis is consumed via different routes of exposure (e.g. smoked, vaporized, edible), POCT devices may not assess all possible routes of exposure.

Overall POC Test Performance

Table 2 shows the results from studies of OF POCT devices included in this review, number of participants), route of administration, and the sensitivity, specificity, and accuracy of the device for detecting marijuana exposure as compared to laboratory-based confirmation methods. In this table, we include the overall results from studies that included both chronic and frequent users, as well as results from the meta-analysis and studies conducted in naturalistic settings (e.g. pubs, bars; individuals arrested for driving impairment).

Scherer and colleagues pooled data from the studies in their meta-analysis to examine performance of individual POCT devices for cannabinoid detection. They found that the DDS2 had a sensitivity of 92.5% and specificity of 92.1%. The DT5000 had a sensitivity of 86.5% and specificity of 95.2%. Two other devices, the DrugWipe5+ and RapidStat also performed well for cannabis detection. The RapidStat was not reviewed in any other studies since Scherer's publication. The DrugWipe5A was examined in one naturalistic setting (social venues) and had low sensitivity (29%) and acceptable specificity (88%) (Stefano Gentili, Solimini, Tittarelli, Mannocchi, & Busardò, 2016). We do not discuss it further in this review.

Among all cannabis users, including frequent and occasional users, and across exposure routes, using a confirmation cut-off of 5ng/mL, the DDS2 had a sensitivity of 84.4% and specificity of 94.5% (Swortwood et al., 2017). The DT5000 had a sensitivity of 80.0% and specificity of 91.9% at the same cut-off (Swortwood et al., 2017). The DDS2 was also tested among individuals arrested for operating a motor vehicle while intoxicated (OWI) and compared to blood test values. Using a cutoff of 25 ng/mL that mirrors the devices own cutoff level, Edwards and colleagues report a sensitivity of 88.4 and specificity of 86.9 (Edwards et al., 2017).

Huestis and colleagues (2013) tested the DT5000 among 24 cannabis users (10 occasional, 14 frequent) and provided information about sensitivity 6-8 hours post-inhalation of smoked cannabis because this time frame is relevant for detecting drivers who may be under the influence of recently used marijuana (Huestis et al., 2013) They found the device sensitivity within 6 and 8 hour time frames was 85.6 and 84.7%, respectively, at the confirmation cutoff of 2ng/mL (SAMHSA). Sensitivity within 6 and 8 hour time frames was 84.0 and 82.5%, respectively, at the cutoff of 1ng/mL (DRUID) (Huestis et al., 2013). This can be interpreted to mean that the DT5000 provides a

positive test result that accurately identifies approximately 85% of cannabis users who are 6-8 hour post smoking, with 15% false negatives (i.e. the test provides a negative results but the individual has THC levels above the confirmation cutoff).

The DRUID project recommended a threshold of 80% sensitivity, 80% specificity, and 80% accuracy has been established as minimum acceptable level of testing performance for a roadside drug screening test. Across all studies, the DT5000 had a sensitivity range from 80.0%-85.5% and specificity range from 82.5%-95.2%. The DDS2 had a sensitivity range from 84.4%-92.5% and specificity range from 86.9-94.5%.

Table 2. Sensitivity and Specificity of Point of Collection Devices for Measuring Cannabis Exposure in Oral Fluid, All Users

Device(s)	Study	Year	N	Age	Population	Exposure route	Comparison Matrix/Method	Cut off value(s)	Sensitivity	Specificity	Accuracy
17 devices including: DDS™, DT5000, Drugwipe™	Scherer et al.	2017	NA (Meta analysis)	NA	Drivers; Drug users; Laboratory participants	Various	Validated chromatographic assay	Not reported	80.5% (7 - 100%)	81.3% (9 - 100%)	41 - 100%
DDS2	Swortwood et al.	2017	545	18-50	Healthy users*	Multiple**	OF (LCMS/MS)	≥ 25 ng/mL ≥ 5 ng/mL ≥ 2 ng/mL ≥ 1n g/L ≥ 0.2 ng/mL	≥ 25 ng/mL =98.5 ≥ 5 ng/mL =84.4 ≥ 2 ng/mL =65.1 ≥ 1 ng/mL =53.2 ≥ 0.2 ng/mL =36.5	≥ 25 ng/mL =84.0 ≥ 5 ng/mL =94.5 ≥ 2 ng/mL =97.6 ≥ 1 ng/mL =98.2 ≥ 0.2 ng/mL =99.2	NA
DDS2	Newmeyer et al.	2017	134	18-50	Healthy users*	Edible	OF and Blood (LCMS/MS)	≥ 25 ng/mL ≥ 10 ng/mL ≥ 5 ng/mL ≥ 2 ng/mL ≥ 1 ng/mL ≥0.2 ng/mL	≥ 25 ng/mL =95.5 ≥ 10 ng/mL =96.0 ≥ 5 ng/mL =96.8 ≥ 2 ng/mL =61.7 ≥ 1 ng/mL =61.7 ≥0.2 ng/mL =44.1	≥ 25 ng/mL =79.5 ≥ 10 ng/mL =81.7 ≥ 5 ng/mL =86.4 ≥ 2 ng/mL =90.5 ≥ 1 ng/mL =90.5 ≥0.2 ng/mL =92.7	NA
DDS2	Edwards et al.	2017	104	18-72	subjects arrested for (OWI)	NA	Blood (Enzyme Immunoassay)	25 ng/mL	88.37	86.89	87.5 PPV: 82.61 NPV: 91.34
DT5000	Swortwood et al.	2017	551	18-50	Healthy Users*	Multiple**	OF (LCMS/MS)	≥ 5 ng/mL ≥ 2 ng/mL ≥1 ng/mL ≥0.2 ng/mL	≥ 5 ng/mL: 80.0 ≥ 2 ng/mL: 66.3 ≥1 ng/mL: 57.5 ≥0.2 ng/mL: 36.9	≥ 5 ng/mL: 91.9 ≥ 2 ng/mL: 96.8 ≥1 ng/mL: 98.7 ≥0.2 ng/mL: 99.3	NA
DT5000	Newmeyer et al.	2017	103	18-50	Healthy Users*	Edible	OF and Blood (LCMS/MS)	≥ 5 ng/mL ≥ 2 ng/mL ≥ 1 ng/mL ≥ 0.2 ng/mL	≥ 5 ng/mL =89.3 ≥ 2 ng/mL =50.0 ≥1 ng/mL =50.0 ≥0.2 ng/mL =34.9	≥ 5 ng/mL =94.7 ≥ 2 ng/mL =97.9 ≥1 ng/mL =97.9 ≥0.2 ng/mL =100	NA
DT5000	Hartman et al.	2015	43	21-42	Healthy users*	Vaporizer	OF (2D-GCMS)	5 ng/mL 2 ng/mL 1 ng/mL	5 ng/mL: 64.9 2 ng/mL: 53.8 1 ng/mL: 48.7	5 ng/mL: 97.2 2 ng/mL: 99.3 1 ng/mL: 100	5 ng/L: 77.5 2 ng/L: 65.0 1 ng/L: 57.1
DT5000	Huestis et al.	2013	24	18-45	Healthy users*	Smoked	OF (2D-GCMS)	2 ng/mL 1 ng/mL	2 ng/mL: 75.3 1 ng/mL: 66.4	2 ng/mL: 94.1 1 ng/mL: 98.9	2 ng/mL: 81.8 1 ng/mL: 73.9
DrugWipe5A	Gentili et al.	2016	83	NA	Subjects in a social setting (e.g. bars)	NA	OF (HS-SPME-GC, MS- EIO)	30 ng/mL	29	88	53

Note: Studies that tested multiple populations and devices may appear more than once. DT5000=Drager™ DrugTest 5000; DDS2= Alere™ DDS2; OF=Oral Fluid; LC-MS/MS=Liquid chromatography – tandem mass spectrometry; 2D-GCMS=Two dimensional gas chromatography-mass spectrometry; HS-SPME-GC=Headspace-Solid Phase Microextraction-Gas Chromatography; MS-EIO= mass spectrometry, electron impact ionization; OWI=operating while intoxicated; *Healthy cannabis users in a laboratory setting; ** multiple routes refers to exposure by controlled smoking, vaporizing, and edible routes in a laboratory setting. The limit of quantitation (LOQ) was 0.2 ng/mL.

Table 3. Sensitivity and Specificity of Point of Collection Oral Fluid Cannabis Exposure Screening Devices, by Cannabis Use Frequency

Device(s)	Study	Year	N	Age	Population	Exposure route	Comparison Matrix/Method	Cut off value(s)	Sensitivity	Specificity
DDS2	Swortwood et al.	2017	345	18-50	Frequent users	Multiple	OF (LCMS/MS)	≥ 25 ng/mL ≥ 5 ng/mL ≥ 2 ng/mL ≥ 1 ng/mL ≥ 0.2 ng/mL	≥ 25 ng/mL =98.0 ≥ 5 ng/mL =85.6 ≥ 2 ng/mL =64.0 ≥ 1 ng/mL =51.6 ≥ 0.2 ng/mL =37.0	≥ 25 ng/mL =82.7 ≥ 5 ng/mL =93.1 ≥ 2 ng/mL =97.9 ≥ 1 ng/mL =98.7 ≥ 0.2 ng/mL =100
DDS2	Newmeyer et al.	2017	72	18-50	Frequent users	Edible	OF and Blood	≥ 25 ng/mL ≥ 5 ng/mL ≥ 2 ng/mL ≥ 1 ng/mL ≥ 0.2 ng/mL	≥ 25 ng/mL =100 ≥ 5 ng/mL =100 ≥ 2 ng/mL =58.8 ≥ 1 ng/mL =58.8 ≥ 0.2 ng/mL =37.0	≥ 25 ng/mL =86.7 ≥ 5 ng/mL =94.5 ≥ 2 ng/mL =100 ≥ 1 ng/mL =100 ≥ 0.2 ng/mL =100
DT5000	Swortwood et al.	2017	300	18-50	Frequent users	Multiple	OF (LCMS/MS)	≥ 5 ng/mL ≥ 2 ng/mL ≥ 1 ng/mL ≥ 0.2 ng/mL	≥ 5 ng/mL =79.1 ≥ 2 ng/mL =65.0 ≥ 1 ng/mL =56.6 ≥ 0.2 ng/mL =39.5	≥ 5 ng/mL =89.5 ≥ 2 ng/mL =97.9 ≥ 1 ng/mL =100 ≥ 0.2 ng/mL =100
DT5000	Newmeyer et al.	2017	60	18-50	Frequent users	Edible	OF and Blood	≥ 5 ng/mL ≥ 2 ng/mL ≥ 1 ng/mL ≥ 0.2 ng/mL	≥ 5 ng/mL =82.4 ≥ 2 ng/mL =43.2 ≥ 1 ng/mL =43.2 ≥ 0.2 ng/mL =30.4	≥ 5 ng/mL =93.0 ≥ 2 ng/mL =95.7 ≥ 1 ng/mL =95.7 ≥ 0.2 ng/mL =100
DDS2	Swortwood et al.	2017	200	18-50	Occasional users	Multiple	OF (LCMS/MS)	≥ 25 ng/mL ≥ 5 ng/mL ≥ 2 ng/mL ≥ 1 ng/mL ≥ 0.2 ng/mL	≥ 25 ng/mL =100 ≥ 5 ng/mL =82.0 ≥ 2 ng/mL =67.7 ≥ 1 ng/mL =57.3 ≥ 0.2 ng/mL =35.4	≥ 25 ng/mL =86.2 ≥ 5 ng/mL =96.7 ≥ 2 ng/mL =97.1 ≥ 1 ng/mL =97.6 ≥ 0.2 ng/mL =98.6
DDS2	Newmeyer et al.	2017	62	18-50	Occasional users	Edible Cannabis	OF and Blood	≥ 25 ng/mL ≥ 5 ng/mL ≥ 2 ng/mL ≥ 1 ng/mL ≥ 0.2 ng/mL	≥ 25 ng/mL =90.0 ≥ 5 ng/mL =92.9 ≥ 2 ng/mL =65.4 ≥ 1 ng/mL =65.4 ≥ 0.2 ng/mL =53.8	≥ 25 ng/mL =71.2 ≥ 5 ng/mL =77.1 ≥ 2 ng/mL =80.6 ≥ 1 ng/mL =80.6 ≥ 0.2 ng/mL =87.0
DT5000	Swortwood et al.	2017	251	18-50	Occasional users	Multiple	OF (LCMS/MS)	≥ 5 ng/mL ≥ 2 ng/mL ≥ 1 ng/mL ≥ 0.2 ng/mL	≥ 5 ng/mL =82.9 ≥ 2 ng/mL =70.8 ≥ 1 ng/mL =60.3 ≥ 0.2 ng/mL =31.5	≥ 5 ng/mL =94.0 ≥ 2 ng/mL =96.1 ≥ 1 ng/mL =97.9 ≥ 0.2 ng/mL =99.2
DT5000	Newmeyer et al.	2017	43	18-50	Occasional users	Edible	OF and Blood	≥ 5 ng/mL ≥ 2 ng/mL ≥ 1 ng/mL ≥ 0.2 ng/mL	≥ 5 ng/mL =100 ≥ 2 ng/mL =63.2 ≥ 1 ng/mL =63.2 ≥ 0.2 ng/mL =44.4	≥ 5 ng/mL =96.9 ≥ 2 ng/mL =100 ≥ 1 ng/mL =100 ≥ 0.2 ng/mL =100

Note: Studies that tested multiple populations and devices may appear more than once. Table reflects same studies and participants as prior table stratified by frequency of cannabis use. Accuracy not available in these studies for these subpopulations. DT5000=Drager™ DrugTest 5000; DDS2= Alere™ DDS2; OF=Oral Fluid; LC-MS/MS=liquid chromatography-tandem mass spectrometry; The limit of quantitation (LOQ) was ~ 0.2 ng/mL.

Chronic Frequent Users versus Occasional Users

Table 3 shows the results from studies testing the accuracy of the OF POCT devices, grouped by participant cannabis use history (e.g. frequent user vs. occasional) and by device. This table reflects the two key studies found by our search that differentiated results based on the participants' cannabis use history. These are the same studies as reported above, but broken out for the subpopulations included rather than overall results.

Swortwood's study for the DDS did not show substantially different performance (e.g. more than few percentage points) between chronic vs. frequent users at a 25ng/mL or 5ng/mL confirmation cutoff. In both groups, sensitivity approached 100% for the 25ng/mL cutoff, and sensitivity was 82%-86%. The same study suggested that at the 5ng/mL cutoff, the DT5000 had a sensitivity of 79.1 for frequent users vs. 82.9 for occasional users; specificity of 89.5 for frequent users vs. 94.0 for occasional users. In their study of smoked cannabis, Huestis et al. report that the sensitivity of the DT5000 was 6-11% higher in frequent as compared to occasional cannabis users and suggest that this was due to having a longer detection windows and higher true positive rates (Huestis et al., 2013; Huestis et al., 2013). The DDS performed slightly better than the DT5000 among frequent users at the 5ng/mL cutoff in the two original studies we reviewed that directly compared the devices. Taking all evidence into account, both devices perform reasonably well for both frequent and occasional users.

Edible Route of Exposure

As shown in Table 3, the DT5000, in a study that focused only on edible cannabis, had a sensitivity of 64.9% and specificity of 97.2%, for an overall accuracy of 77.5% (Hartman et al., 2015). A smaller study found a sensitivity of 89.3 and specificity of 94.7. This is in contrast to the DDS2 which, in the smaller study, had a sensitivity of 96.8 and specificity of 86.5. The DT5000 may perform slightly better than the DDS2 when edible cannabis has been consumed, as its specificity was higher (96.9% vs. 77.1%) in the study by Newmeyer and colleagues that focused on the edible route of exposure (Newmeyer et al., 2017a).

Vaporized Route of Exposure

Hartman and colleagues (2015) reported that the DT5000 showed sensitivity of 64.9, specificity of 97.2, and efficiency of 77.5% after vaporized cannabis, using the 5ng/mL confirmatory cutoff (Hartman et al., 2015). These authors noted that cannabis vapor may interact with oral mucosa differently to smoke, altering the performance of the POCT (Hartman et al., 2015). While the sensitivity in this study was reduced due to false negatives compared to other studies that tested the device after smoked or edible routes of administration, the high specificity indicates that false positives were rare.

POC Urine Testing

One study returned by our searches evaluated POTC urine tests, the EZ Cup and the Multi4Card (Kim et al., 2017). The study utilized commercially available samples (Detectabase) and information about the individuals who originally provided the samples was not available. The cut-off value for these tests was 50 ng/mL of THC-COOH. The results were assessed on a grading scale (G2-G4) where lower grade meant a higher drug concentration for confirmation testing. The EZ Cup had a sensitivity ranging from 98.5 (G2) to 100 (G4) and a specificity ranging from 93.0 (G2) to 53.0 (G4). The Multi4Card had a sensitivity range from 6.0 (G2) to 92.0 (G4) and a specificity range from 99.2 (G2) to 87.7 (G4). The EZ cup had with consistently low false negative tests, but, as concentration decreased, there were more false positives. The EZ Cup therefore exhibited better performance, but it is important to note that the inactive metabolite THC-COOH can be detected for days to weeks after cannabis administration (Goodwin et al., 2008) and a positive screening result alone (absent other information) does not permit inference regarding time of cannabis use.

Other Considerations

Across all studies, authors note that frequent smokers had significantly later median t_{last} (time of last cannabis detection) compared to occasional smokers. This means that frequent marijuana users may show positive results on POCT results for longer after cannabis administration compared to occasional users who used the same amount.

The studies described here utilize THC as the confirmation marker of cannabis exposure. Hartman (2015) and colleagues note that THC-COOH has been proposed as a potential additional confirmatory criterion, to be used with THC because it helps rule out passive environmental exposure, detects oral cannabis use, and can extend detection windows in chronic frequent cannabis smokers (Lee et al., 2011; Moore et al., 2011). However, in Hartman's study of vaporized cannabis, THCCOOH was not always detected; including THCCOOH as a requirement for confirmation decreased sensitivity. At this point, the use of additional metabolites as a confirmatory method with POCT devices is not firmly established in the literature.

Research Question 3a: Cognitive and Behavioral Effects Relevant to Driving

We reviewed 29 studies that contained information about the cognitive and behavioral indicators of marijuana exposure that are relevant to operating a motor vehicle. The study designs utilized can be grouped into four categories: laboratory studies, studies conducted in a driving simulator, on-road studies, and observational studies. The cognitive and behavioral effects of marijuana that relate to driving fall into three domains which include automotive behavior, control behavior, and executive function/planning. These domains were described in Walsh's 2008 Guidelines for Research on Drugged Driving (Walsh et al., 2008). Based on the literature we obtained through our search, for the purpose of this review, we address an additional behavioral domain which is driving performance/safety. Table 4 describes the domains and provides examples of tasks/tests that measure them.

Multiple effects may be measured in one study, and different study designs are well-suited to evaluate different types of effects. For example, only the simulator and on-road studies can address driving performance and safe driving. We also considered the elements of the standardized field sobriety test (SFST) which is reflective of control behavior. The SFST includes activities such as a one leg stand, walk and turn, and the modified Romberg balance test.

Table 4. Domains of Driving-Related Cognitive and Behavioral Effects of Marijuana

Domain	Definition	Example Tasks Used for Measurement
Automotive Behavior*	Well-learned skills	<ul style="list-style-type: none"> Tracking, steering (road tracking, critical tracking, compensatory tasks). Vigilance or sustained attention (e.g. Mackworth Clock Test).
Control Behavior*	Maintaining distance, passing, etc.	<ul style="list-style-type: none"> Motor performance, maneuvers (reaction time, car following tasks). Divided attention (dual attention tasks). Perception (time to collision-type tasks).
Executive Function/Executive Planning *	Interactive functions with ongoing traffic.	<ul style="list-style-type: none"> Risk taking, impulsivity (e.g. stop signal, Iowa gambling tasks). Information processing, attention (choice, reaction time, selective or focused attention tasks). Cognition, judgement
Driving performance/safety	Appropriate and safe operation of a vehicle	<ul style="list-style-type: none"> Maintaining proper headway Lane positioning Speed and braking
Note: *Definitions from Walsh et al. 2008 "Guidelines for Research on Drugged Driving"		

Automotive Behavior

In lab-based studies, we found evidence for 15 different measurements of automotive behavior across 6 studies. For frequent users, 5 out of 6 saw no effect, and 1 found hurt performance, although it must be noted that two of these studies included low doses of cannabis. For occasional users, 5/5 tests indicated that marijuana hurt performance. In 4 studies in which the population cannabis use history was not specified, both low and medium dose administration resulted in generally worse task performance (3/4). Two simulator studies that included measurement of automotive behavior both found decreased performance after marijuana administration.

Table 5. Assessments of the Impact of Cannabis Exposure on Automotive Behavior

Study	Study Type	n	User Population	THC Dosage (Route)	Brief description	Result*	Magnitude of Result*	Study Quality**
Weinstein et al. 2008	Lab	14	Frequent	13 and 17 mg	Virtual Maze task	HP	NA	SS, NT
Desroisiers et al. 2015	Lab	25	Frequent	6.80%	CTT	NE	NA	SS
Shwope et al. 2012	Lab	10	Frequent	6.80%	CTT	NE	NA	LD, SS
Shwope et al. 2012	Lab	10	Frequent	6.80%	Divided Attention Task	NE	NA	LD, SS
Ramaekers et al. 2011	Lab	21	Frequent	(~28mg)	Tracking Task	NE	NA	SS, LD,
Ramaekers et al. 2009	Lab	12	Frequent	~35mg)	CTT	NE	NA	SS
Sexton et al. 2000	Lab	15	NS	1.7% - 2.67%	Critical Tracking Task	HP	NA	SS, LD, UP
Ramaekers et al. 2006	Lab	20	NS	17.5mg (4%)	Tracking Task	HP	NA	SS, LD, UP
Ramaekers et al. 2006	Lab	20	NS	35mg (13%)	Tracking Task	HP	NA	SS, UP
Sexton et al. 2000	Lab	15	NS	1.7% - 2.67%	Critical Tracking Task	NE	NA	SS, LD UP
Desroisiers et al. 2015	Lab	25	Occasional	6.80%	CTT	HP	NA	SS
Batistella et al. 2013	Lab	31	Occasional	42mg	CTT	HP	NA	SS
Batistella et al. 2013	Lab	31	Occasional	42mg	FMRI (tracking)	HP	NA	SS
Batistella et al. 2013	Lab	31	Occasional	42mg	FMRI (target & cursor)	HP	NA	SS
Ramaekers et al. 2009	Lab	12	Occasional	~35mg	CTT	HP	NA	SS
Papafotiou et al. 2005	Sim.	40	NS	14mg & 52mg	Tracking Task	HP	NA	UP
Menetrey et al. 2005	Sim.	8	Occasional	16.5mg & 45.7mg (oral)	Tracking Task	HP	NA	SS, NT

Note: NS=not specified; CTT=critical tracking task; *Result classified as: HP=hurt performance, IP=improved performance, NE=no effect. Magnitude of results only provided if statically significant. ** Issues potentially impacting study quality were noted as: SS=small sample size; NT = no validated tool used; LD = low dose marijuana, UP=user population not defined, DR= use of subjective high with no dose response gradient; OT=other quality issues. Sim.= Driving simulator study.

Control Behavior

In 18 lab-based measurements of control behavior, 11 focused on frequent or not specified user population, and 4 observed poorer performances after marijuana administration, 1 with improved performance, and 6 with no effect. Of note, the largest study had 136 participants and demonstrated poorer performance. Among tests in occasional users, 6/7 demonstrated poorer performance with one demonstrating no effect. Simulator-based studies showed an even split between hurt performance and no

effect. In three on-road studies, control behavior, and specifically reaction time, was not impacted.

In lab studies, 9/9 tests that used elements of the SFST to assess control behavior among frequent users demonstrated no effect. In occasional users, this was 3/9. And in two observational studies that together accounted for results on seven tests of control behavior as measured with a SFST, decreased performance was noted in all tests, though it must be noted that the study design did not allow assessment of most potential limitations.

Executive Function and Planning

In 16 tests of executive function among frequent cannabis users, six hurt performance and 10 showed no effect. Among occasional users, six hurt performance, and six showed no effect. For non-specified users, 9/10 studies showed hurt performance. These results indicate more evidence for decreased executive function regardless of use history, with about half or more of the studies finding decreased performance.

Driving Performance and Safety

In simulator studies, mean speed decreased in 6/14 studies conducted among occasional users. We did not characterize decreased speed as either an improvement or detriment to driving performance, since in a real-world environment this behavior could be associated either with safer driving or with an increased crash risk, depending on the circumstance. There were three studies with decreased performance, including on a measure of collisions, and all other results showed no effect. In two studies that did not specify the cannabis use history of participants, there was decreased performance on 5/7 measures. These included mean headway and lateral position, and speed measures. In 10 driving performance tasks conducted in on-road studies of occasional users, the authors observed impaired performance for five tasks and no effect for five tasks.

Table 6. Assessments of the Impact of Cannabis Exposure on Control Behavior

Study	Study Type	n	User Population	THC Dosage (Route)	Brief description	Result	Result Magnitude*	Study Quality
Ramaekers et al. 2000	On-road	18	NS	100 and 200 ng/kg	Reaction time	NE	NA	SS, UP
Robbe et al. 1998 # 2	On-road	16	Occasional	100, 200, 300 ng/kg	Reaction time	NE	NA	SS
Robbe et al. 1998 # 4	On-road	18	Occasional	100 and 200 ng/kg	Reaction time	NE	NA	SS
Lenne et al. 2009	Simulator	47	NS	19mg & 38mg	Sign detection task	HP	NA	UP
Sexton et al. 2000	Simulator	15	NS	1.7% & 2.6%	Reaction time task	NE	NA	SS, UP
Ronen et al. 2010	Simulator	12	Occasional	13mg	Arithmetic Task	HP	NA	SS, NT
Ronen et al. 2007	Simulator	14	Occasional	13mg & 17mg	Reaction time test - Computerized	HP	S	SS, NT
Rafaelsen et al. 1973	Simulator	8	Occasional	200, 300, 400mg	Reaction Time	HP	NA	SS
Anderson et al. 2010	Simulator	85	Occasional	22.9mg	Paced Auditory Serial-Addition Test [PASAT]	HP	M	
Anderson et al. 2010	Simulator	85	Occasional	22.9mg	Emergency Vehicle Avoidance Task	NE	NA	
Anderson et al. 2010	Simulator	85	Occasional	22.9mg	Dog and intersection Incursion Task, PASAT Task, Emergency vehicle avoidance task	NE	NA	
Anderson et al. 2010	Simulator	85	Occasional	22.9mg	Emergency Vehicle Avoidance Task	NE	NA	
Metrik et al. 2012	Lab	136	Frequent	2.80%	Stroop test	HP	M	LD
Hart et al. 2001	Lab	18	Frequent	1.8% & 3.9%	Repeated Acquisition Task (Computerized)	HP	NA	SS, LD
Ramaekers et al. 2011	Lab	21	Frequent	~28mg	Divided Attention Task	HP	NA	SS, LD
Theunissen et al. 2012	Lab	24	Frequent	13%	Electro Cap / Neuro Scan Software	HP	S	SS
Hart et al. 2001	Lab	18	Frequent	1.8% & 3.9%	Divided Attention Task	IP	NA	SS, LD
Shwope et al. 2012	Lab	10	Frequent	6.80%	DAT - Computerized	NE	NA	LD, SS
Shwope et al. 2012	Lab	10	Frequent	6.80%	DAT - Computerized	NE	NA	LD, SS
Theunissen et al. 2012	Lab	24	Frequent	13%	DAT - Computerized	NE	NA	SS
Ramaekers et al. 2009	Lab	12	Frequent	~35mg	Divided Attention Task	NE	NA	SS
Desroisers et al. 2015	Lab	25	Frequent	6.80%	Divided Attention Task	NE	NA	SS
Theunissen et al. 2012	Lab	24	Frequent	13%	Electro Cap / Neuro Scan Software	HP	M	SS
Chiat 1994	Lab	14	NS	3.60%	Time Production Test	NE	NA	SS, LD, UP
Chiat 1994	Lab	14	NS	3.60%	Divided Attention Task	NE	NA	SS, LD, UP
Desroisers et al. 2015	Lab	25	Occasional	6.80%	Divided Attention Task	HP	NA	SS
Theunissen et al. 2012	Lab	24	Occasional	13%	DAT - Computerized	HP	S	SS
Theunissen et al. 2012	Lab	24	Occasional	13%	Electro Cap / Neuro Scan Software	HP	S	SS
Theunissen et al. 2012	Lab	24	Occasional	13%	Electro Cap / Neuro Scan Software	HP	S	SS
Ramaekers et al. 2009	Lab	12	Occasional	~35mg	Divided Attention Task	HP	NA	SS

Note: DAT=divided attention task; *Result classified as: HP=hurt performance, IP=improved performance, NE=no effect. Magnitude of results only provided if statically significant. ** Issues potentially impacting study quality were noted as: SS=small sample size; NT = no validated tool used; LD = low dose marijuana, UP=user population not defined, DR= use of subjective high with no dose response gradient; OT=other quality issues.

Table 7. Assessments of the Impact of Cannabis Exposure on Executive Function and Planning Behavior

Study	Study Type	n	User Population	THC Dosage (Route)	Brief description	Result	Result Magnitude*	Study Quality
Metrik et al. 2012	Lab	136	Frequent	2.80%	Stop Signal Task	HP	M	LD
Weinstein et al. 2008	Lab	14	Frequent	13 and 17 mg	Wisconsin Card Sorting Task	HP	NA	SS, NT
Weinstein et al. 2008	Lab	14	Frequent	13 and 17 mg	Gambling Task	HP	M	SS, NT
Theunissen et al. 2012	Lab	24	Frequent	500 ng/kg (13%)	Stop Signal Task - computerized	HP	M	SS
Ramaekers et al. 2009	Lab	12	Frequent	500ng/kg (~35mg)	Stop Signal Task	HP	NA	SS
Hart et al. 2001	Lab	18	Frequent	1.8% & 3.9%	Digit Recall Task (Computerized)	HP (3.9%)	NA	SS, LD
Vadhan et al. 2006	Lab	36	Frequent	1.8 & 3.9%	Gambling Task	NE	NA	LD, DR
Desroisiers et al. 2015	Lab	25	Frequent	6.80%	n-back task	NE	NA	SS
Desroisiers et al. 2015	Lab	25	Frequent	6.80%	Balloon Analog Task	NE	NA	SS
Sewell et al. 2012	Lab	44	Frequent	0.015 - 0.05 mg/kg	Time Estimation	NE	NA	LD, DR
Hart et al. 2001	Lab	18	Frequent	1.8% & 3.9%	Digit Symbol Substitution Task	NE	NA	SS, LD
Weinstein et al. 2008	Lab	14	Frequent	13 and 17 mg	Novel TP task	NE	NA	SS, NT
Ramaekers et al. 2011	Lab	21	Frequent	400 ng/kg (~28mg)	Stop Signal Task	NE	NA	SS, LD
Ramaekers et al. 2011	Lab	21	Frequent	400 ng/kg (~28mg)	Tower of London Task	NE	NA	SS, LD
Ramaekers et al. 2009	Lab	12	Frequent	500ng/kg (~35mg)	Tower of London Task	NE	NA	SS
Chiat 1994	Lab	14	NS	3.60%	Backward Digit Span	HP	NA	SS, LD, UP
Ramaekers et al. 2006	Lab	20	NS	17.5mg (4%)	Stop Signal Task	HP	NA	SS, LD, UP
Ramaekers et al. 2006	Lab	20	NS	17.5mg (4%)	Tower of London Task	HP	NA	SS, LD, UP
Ramaekers et al. 2006	Lab	20	NS	17.5mg (4%)	Gambling task	HP	NA	SS, LD, UP
Ramaekers et al. 2006	Lab	20	NS	35mg (13%)	Stop Signal Task	HP	NA	SS, UP
Ramaekers et al. 2006	Lab	20	NS	35mg (13%)	Tower of London Task	HP	NA	SS, UP
Ramaekers et al. 2006	Lab	20	NS	35mg (13%)	Gambling task	HP	NA	SS, UP
Chiat 1994	Lab	14	NS	3.60%	Digit Symbol Substitution Task	NE	NA	SS, LD, UP
Lane et al. 2005	Lab	10	NS	1.77% & 3.5%	Computerized gambling ask	HP	S	SS, LD, UP
Desroisiers et al. 2015	Lab	25	Occasional	6.80%	n-back task	NE	NA	SS
Desroisiers et al. 2015	Lab	25	Occasional	6.80%	Balloon Analog Task	NE	NA	SS
Sewell et al. 2012	Lab	44	Occasional	0.015 - 0.05 mg/kg	Time Estimation Software 2.0	HP	M	LD, DR
MacDonald et al. 2003	Lab	37	Occasional	15mg (Oral)	Verbal Digit Span Task	HP	NA	
MacDonald et al. 2003	Lab	37	Occasional	15mg (Oral)	time perception task	HP	NA	
MacDonald et al. 2003	Lab	37	Occasional	15mg (Oral)	Computerized Stop Signal Task	HP	NA	
Theunissen et al. 2012	Lab	24	Occasional	500 ng/kg (13%)	Stop Signal Task - computerized	HP	S	SS
Ramaekers et al. 2009	Lab	12	Occasional	500ng/kg (~35mg)	Stop Signal Task	HP	NA	SS
MacDonald et al. 2003	Lab	37	Occasional	15mg (Oral)	Delay Discounting Task	NE	NA	SS, LD
Ramaekers et al. 2009	Lab	12	Occasional	500ng/kg (~35mg)	Tower of London Task	NE	NA	SS
MacDonald et al. 2003	Lab	37	Occasional	15mg (Oral)	Hopkins Verbal Recall Task	NE	NA	
MacDonald et al. 2003	Lab	37	Occasional	15mg (Oral)	Verbal Go no go task	NE	NA	

Note: DAT=divided attention task; *Result classified as: HP=hurt performance, IP=improved performance, NE=no effect. Magnitude of results only provided if statically significant. ** Issues potentially impacting study quality were noted as: SS=small sample size; NT = no validated tool used; LD = low dose marijuana, UP=user population not defined, DR= use of subjective high with no dose response gradient; OT=other quality issues.

Research Question 3b: Field Measurement of Marijuana's Effects and Accuracy for Determining Impairment

Laboratory based measurement of marijuana's cognitive and behavioral effects are described above. While there are many tools used to measure the domains of impairment in laboratory settings, as evidenced in Tables 5-7, field measures lag behind.

In the peer reviewed literature, we identified three studies testing SFST for detecting marijuana impairment. Accuracy was, at best approximately 50% for the one leg stand portion of the test. We also conducted a web search that identified several mobile applications that offer versions of some of the tests for automative behavior, executive function, and control behavior that were measured above, as being impacted by marijuana. Although only one tool: DRUID (Milburn, 2017), was developed explicitly for measuring marijuana-related effects, these tools in general may have promise. DRUID is being tested in an NIH-funded study at Brown University Medical School.

Table 8. Field Tests for Cognitive and Behavioral Indicators of Marijuana Effects, Peer-Reviewed Literature

Tool Type	Tested for MJ	Study	Year	Accuracy for MJ Impairment	Overall Result
SFST	Yes	Porath-Waller and Beirness	2014	Classification Rate: HGN: 1% OLS: 55.4%* WAT: 39.7%	Cannabis adversely affected performance on the OLS test but not the WAT and HGN tests
SFST	Yes	Bosker et al.	2012	HGN: 15% OLS: 50%* WAT: 35%	Cannabis significantly impaired performance on the OLS
SFST	Yes	Papafotiou	2005	Overall SFST Battery: Time 1 (5 min post smoking): 46.2% Time 2 (55 min post smoking): 41% Time 3 (105 min post smoking): 28.2%	The results indicated that the consumption of cannabis containing either 1.74% THC or 2.93% THC impaired performance on the SFSTs.

Notes: HGN=horizontal gaze nystagmus; WAT=Walk and Turn; OLS= one leg stand

Table 9. Field Tests of Cognitive and Behavioral Indicators of Marijuana’s Effects, Non-Peer Reviewed

Tool Type	Tool Name	Designed for MJ	Relates to R3A Task Category / Test	URL	Notes
Mobile App	DRUID	Yes	Automotive behavior; Executive function; Control behavior o Reaction time o Decision making o Tracking o Time estimation	https://www.druidapp.com	"DRUID is currently being tested in a NIH-funded study at the Brown University Medical School."
Mobile App	Brain Turk	No	Automotive behavior; Control behavior o Go -no go task o N Back task o Tracking o Digit tasks o Wisconsin card sorting task o Gambling / risk taking task o Recall tasks o Arithmetic task o Audio vision matching o Complex working memory o Advertises 40+ games / available tests on mobile app	https://www.brain-turk.com/games	Advertised as cognitive games. Not meant to assess exposure to MJ. Included given mobile availability of many of the task category tests identified in RQ3A
Mobile App	Encephal-app	No	Control behavior - Stroop Test	http://www.encephalapp.com	Not meant to assess exposure to MJ. Included given mobile availability of task category tests identified in RQ3A
Mobile App	CANTAB	No	Control behavior - Stop Signal Task - Gambling Task	http://www.cambridgecognition.com/cantab/	Not meant to assess exposure to MJ. Included given mobile availability of task category tests identified in RQ3A
Mobile App	Brain Baseline	No	Control behavior - Stroop Test - N-Back	https://itunes.apple.com/us/app/brain-baseline/id408975136?mt=8	Not meant to assess exposure to MJ. Included given mobile availability of task category tests identified in RQ3A

Discussion

Well-established laboratory methods for quantifying marijuana exist and offer high sensitivity and specificity for measurement of delta-9-THC. Among the most popular techniques currently in use are chromatographic methods such as gas chromatography mass spectrometry (GC-MS) and liquid chromatography with tandem mass spectrometry (LC-MS/MS). In relation to quantifying exposure, the absence of ability to discern potentially key pieces of information from measuring THC alone however has spurred interest in the utility of THC metabolite quantification. The phase-two THC metabolite (THC-Glucuronide) as well as cannabigerol (CBG), cannabiol (CBN), and tetrahydrocannabivarin (THCV) offer promise in discerning recency of use and movement of metabolites to alternative matrices (Huestis & Smith, 2018). As research related to marijuana metabolism continues to advance, such inferences may prove useful in efforts to establish legal driving limits and standards. Despite this promise however, the inability to quantify THC metabolites in a field setting remains a chief limitation.

This review identified two point-of-collection devices with substantial evidence that they perform with sensitivity and specificity above 80% at a confirmation cut-point of 5ng/mL. The DT5000 has a slightly lower sensitivity and higher specificity; the DDS2 has a slightly higher sensitivity and lower specificity. Most screening tests require tradeoffs between these two aspects of correct identification. A higher sensitivity reduces false negatives (i.e. a cannabis user with delta-9-THC above the cut-off who screens negative); a higher specificity reduces false positives (e.g. an individual with a delta-9-THC level below the cut-off who screens positive). Choice between the two devices should depend upon the specific use case and consequences of misclassification. The findings from this study indicate that OF devices may be effective for use in field settings with reasonable accuracy.

For context, recent studies showed that after smoking or vaporizing cannabis in a controlled environment, chronic frequent users maintained blood THC levels of 25 ng/mL for an average of ~ 30-45 minutes. By ~6-10 hours, levels have fallen to 5 ng/mL and at 72 hours post smoking, blood THC levels remained between 5 ng/mL and the LOQ (1 ng/mL) (Newmeyer et al., 2016). Frequent users that orally ingested cannabis in a controlled environment showed similar long term pharmacokinetic profiles, with blood THC levels between 5 ng/mL and the LOQ (1 ng/mL) 72 hours post ingestion. However, average peak concentrations were lower (~25ng/mL) and average time to peak concentration (~ 3-4 hours) was greater with average blood levels remaining under 10 ng/mL leading up to the peak (Newmeyer et al., 2017a; Newmeyer et al., 2016).

In occasional users, THC blood levels in controlled environments after smoking and vaporization peaked on average in ~10 minutes and stayed above 25 ng/mL for ~30 minutes. At approximately one hour, THC levels remained close to 5 ng/mL but by ~ 3 hours on average, THC blood levels had fallen below the LOQ and by ~ 12-15 hours, THC was undetectable (Newmeyer et al., 2016). Blood THC levels of occasional users ingesting THC in a controlled environment followed a similar peaking pattern to that of frequent users. On average, concentrations did not peak until ~ 3 hours post ingestion.

However, by ~ 5 hours blood THC levels had fallen below 5ng/mL and by ~ 11 hours, THC was not detectable in the blood (Newmeyer et al., 2016).

Blood cannabinoid concentration cannot be estimated from OF data (Newmeyer et al., 2017b). The studies reviewed indicated that for smoked and vaporized cannabis, OF and blood THC concentrations were significantly correlated for up to 8 hours cannabis administration (Hartman et al., 2016), with THC concentrations in both matrices peaking during or shortly after use followed by rapid decreases. Edible cannabis, however, displays a different profile with OF THC C_{max} (maximum concentration) occurring by 0.3 hours, while blood THC C_{max} occurs 1-5 hours later. These different pharmacokinetic time courses explain the lack of correlation between OF and blood concentrations during the first 5 h after edible cannabis (Newmeyer et al., 2017b). Thus, the route of cannabis administration has a large impact on how well oral fluid correlates with blood THC. At present, most marijuana users smoke or vaporize marijuana, making oral fluid testing a reasonable option, though other routes of administration may become more frequent as retail sales of adult use marijuana begin in Massachusetts.

The evidence suggests that marijuana has cognitive and behavioral effects in the areas of automative behavior, especially for occasional users, and there also are likely some executive function impacts for some users. In simulated road environments, marijuana exposure was associated with decreased speed; which may be either positive or negative for driving performance and crash risk, depending on the circumstance. Marijuana exposure also unquestionably hurt driving performance in some ways. The overall picture was one of mixed results that on balance fall between no effect and decreased performance. It is worth noting that when reported, magnitude of impaired performance was generally small. In controlled environments, the marijuana use was not associated with performance decreases on elements of the standardized field sobriety test, though observational studies reached a different conclusion.

References

- Alcohol and Drug Abuse Institute. (2013). What is Cannabis? Retrieved from <http://learnaboutmarijuanawa.org/factsheets/whatiscannabis.htm>.
- Alere DDS®2 Mobile Test System: Rapid Screening for Drugs of Abuse in Oral Fluid. (2018). Retrieved from <https://www.alere.com/en/home/product-details/dds2-mobile-test-system.html#>.
- Allen, K. R. (2011). Screening for drugs of abuse: which matrix, oral fluid or urine? *Annals of Clinical Biochemistry*, 48(6), 531-541.
- Arnett, J. J., & Tanner, J. L. (Eds.). (2004). *Emerging Adulthood: The Winding Road from the Late Teens through the Twenties*. New York, NY: Oxford University Press.
- Arria, A. M., Caldeira, K. M., Vincent, K. B., Garnier-Dykstra, L. M., & O'Grady, K. E. (2011). Substance-related traffic-risk behaviors among college students. *Drug Alcohol Depend*, 118(2-3), 306-312. doi:10.1016/j.drugalcdep.2011.04.012
- Asbridge, M., Hayden, J. A., & Cartwright, J. L. (2012). Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *BMJ*, 344, e536.
- Banta-Green, C., Rowhani-Rahbar, A., Ebel, B. E., Andris, L. M., & Qiu, Q. (2016). Cannabis Use among Drivers Suspected of Driving Under the Influence or Involved in Collisions: Analyses of Washington State Patrol Data.
- Berning, A., & Smither, D. (2014). *Understanding the Limitations of Drug Test Information, Reporting, and Testing Practices in Fatal Crashes*. Washington, D.C.: U. S. D. o. Transportation.
- Blencowe, T., Pehrsson, A., & Lillsunde, P. (2010). *Analytical evaluation of oral fluid screening devices and preceding selection procedures*. A. a. M. Driving Under the Influence of Drugs. Retrieved from https://www.bast.de/Druid/EN/deliverables-list/downloads/Deliverable_3_2_2.pdf?_blob=publicationFile&v=1.
- Bondallaz, P., Favrat, B., Chtioui, H., Fornari, E., Maeder, P., & Giroud, C. (2016). Cannabis and its effects on driving skills. *Forensic Sci Int*, 268, 92-102. doi:<https://doi.org/10.1016/j.forsciint.2016.09.007>.
- Bosker, W. M., & Huestis, M. A. (2009). Oral fluid testing for drugs of abuse. *Clin Chem*, 55(11), 1910-1931.
- Chihuri, S., Li, G., & Chen, Q. (2017). Interaction of marijuana and alcohol on fatal motor vehicle crash risk: a case-control study. *Inj Epidemiol*, 4(1), 8. doi:10.1186/s40621-017-0105-z.
- Compton, R. (2017). *Marijuana-Impaired Driving A Report to Congress*. Washington, DC.
- Davis, K. C., Allen, J., Duke, J., Nonnemaker, J., Bradfield, B., Farrelly, M. C., . . . Novak, S. (2016). Correlates of Marijuana Drugged Driving and Openness to Driving While High: Evidence from Colorado and Washington. *PLoS One*, 11(1), e0146853. doi:10.1371/journal.pone.0146853.
- Department of Health and Environment, C. Adult marijuana use trends. *Monitoring trends in adult marijuana use*.
- Department of Health and Human Services. (2015). *Mandatory Guidelines for Federal Workplace Drug Testing Programs*.
- Dräger DrugTest® 5000: Analysis system for detecting drugs. (2018). Retrieved from https://www.draeger.com/Library/Content/drugtest_5000_pi_9041006_en.pdf.
- Drummer, O. H. (2010). Forensic toxicology. *Exs*, 100, 579-603.
- Edwards, L. D., Smith, K. L., & Savage, T. (2017). Drugged Driving in Wisconsin: Oral Fluid Versus Blood. *J Anal Toxicol*, 41(6), 523-529. doi:10.1093/jat/bkx051.
- Gentili, S., Solimini, R., Tittarelli, R., Mannocchi, G., & Busardo, F. P. (2016). A Study on the Reliability of an On-Site Oral Fluid Drug Test in a Recreational Context. *J Anal Methods Chem*, 2016, 1234581. doi:10.1155/2016/1234581.

- Gentili, S., Solimini, R., Tittarelli, R., Mannocchi, G., & Busardò, F. P. (2016). A Study on the Reliability of an On-Site Oral Fluid Drug Test in a Recreational Context. *J Anal Methods Chem*, 2016, 1234581. doi:10.1155/2016/1234581.
- Goodwin, R. S., Darwin, W. D., Chiang, C. N., Shih, M., Li, S.-H., & Huestis, M. A. (2008). Urinary elimination of 11-nor-9-carboxy-delta9-tetrahydrocannabinol in cannabis users during continuously monitored abstinence. *Journal of analytical toxicology*, 32(8), 562-569.
- Grotenhermen, F. (2003). Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*, 42(4), 327-360. doi:10.2165/00003088-200342040-00003.
- Gunasekaran, N., Long, L. E., Dawson, B. L., Hansen, G. H., Richardson, D. P., Li, K. M., . . . McGregor, I. S. (2009). Reintoxication: the release of fat-stored $\Delta(9)$ -tetrahydrocannabinol (THC) into blood is enhanced by food deprivation or ACTH exposure. *British Journal of Pharmacology*, 158(5), 1330-1337. doi:10.1111/j.1476-5381.2009.00399.x.
- Hartman, R. L., Anizan, S., Jang, M., Brown, T. L., Yun, K. M., Gorelick, D. A., . . . Huestis, M. A. (2015). Cannabinoid disposition in oral fluid after controlled vaporizer administration with and without alcohol. *Forensic Toxicology*, 33(2), 260-278. doi:10.1007/s11419-015-0269-6.
- Hartman, R. L., Brown, T. L., Milavetz, G., Spurgin, A., Gorelick, D. A., Gaffney, G., & Huestis, M. A. (2016). Controlled vaporized cannabis, with and without alcohol: subjective effects and oral fluid-blood cannabinoid relationships. *Drug Test Anal*, 8(7), 690-701. doi:10.1002/dta.1839.
- Hoffman, J. (2016). Study finds sharp increase in marijuana exposure among Colorado children. *The New York Times*. Retrieved from <https://www.nytimes.com/2016/07/26/health/marijuana-edibles-are-getting-into-colorado-childrens-hands-study-says.html>.
- Hollister, L. E., Gillespie, H. K., Ohlsson, A., Lindgren, J. E., Wahlen, A., & Agurell, S. (1981). Do plasma concentrations of delta 9-tetrahydrocannabinol reflect the degree of intoxication? *J Clin Pharmacol*, 21(8-9 Suppl), 171s-177s.
- Huestis, M. A. (2002). Cannabis (Marijuana) - Effects on Human Performance and Behavior. *Forensic Sci Rev*, 14(1-2), 15-60.
- Huestis, M. A. (2007). Human Cannabinoid Pharmacokinetics. *Chemistry & biodiversity*, 4(8), 1770-1804. doi:10.1002/cbdv.200790152.
- Huestis, M. A., Milman, G., Mendu, D., Lee, D., Barnes, A. J., Schwoppe, D., . . . Desrosier, N. A. (2013). *Evaluation the on-site Draeger DrugTest 5000 in occasional and chronic frequent smokers following controlled cannabis smoking*. Retrieved from http://www.icadtsinternational.com/files/documents/2013_058.pdf.
- Huestis, M. A., Milman, G., Mendu, D., Lee, D., Barnes, A. J., Schwoppe, D. M., . . . Desrosiers, N. A. (2013). *Evaluation of the on-site Draeger DrugTest 5000 in occasional and chronic frequent smokers following controlled cannabis smoking*. Paper presented at the International Conference on Alcohol, Drugs and Traffic Safety (T2013), 20th, 2013, Brisbane, Queensland, Australia.
- Huestis, M. A., & Smith, M. L. (2018). Cannabinoid Markers in Biological Fluids and Tissues: Revealing Intake. *Trends Mol Med*, 24(2), 156-172. doi:10.1016/j.molmed.2017.12.006.
- Kim, S. Y., Kim, H., Park, Y., Lim, J., Kim, J., Koo, S. H., & Kwon, G. C. (2017). Evaluation of an Automated Reader and Color Interpretation-Based Immunoassays for Multiplexed Drug-of-Abuse Testing in Urine. *J Anal Toxicol*, 41(5), 412-420. doi:10.1093/jat/bkx014.
- Lee, D., Milman, G., Barnes, A. J., Goodwin, R. S., Hirvonen, J., & Huestis, M. A. (2011). Oral fluid cannabinoids in chronic, daily cannabis smokers during sustained, monitored abstinence. *Clin Chem*, 57(8), 1127-1136.

- Li, G., Chihuri, S., & Brady, J. E. (2017). Role of alcohol and marijuana use in the initiation of fatal two-vehicle crashes. *Annals of Epidemiology*, 27(5), 342-347.e341. doi:<https://doi.org/10.1016/j.annepidem.2017.05.003>.
- Li, K., Simons-Morton, B., Gee, B., & Hingson, R. (2016). Marijuana-, alcohol-, and drug-impaired driving among emerging adults: Changes from high school to one-year post-high school. *J Safety Res*, 58, 15-20. doi:10.1016/j.jsr.2016.05.003.
- Macdonald, S., Anglin-Bodrug, K., Mann, R. E., Erickson, P., Hathaway, A., Chipman, M., & Rylett, M. (2003). Injury risk associated with cannabis and cocaine use. *Drug Alcohol Depend*, 72(2), 99-115.
- Milburn, M. (2017). DRUID. Retrieved from <https://www.druidapp.com>.
- Moore, C., Coulter, C., Uges, D., Tuyay, J., Van der Linde, S., Van Leeuwen, A., . . . Orbita Jr, J. (2011). Cannabinoids in oral fluid following passive exposure to marijuana smoke. *Forensic Sci Int*, 212(1-3), 227-230.
- National Highway Traffic Safety Administration. (2016a). *2016 FARS/CRSS Coding and Validation Manual*. Washington, D.C: National Highway Traffic Safety Administration. Retrieved from <https://crashstats.nhtsa.dot.gov/Api/Public/Publication/812449>.
- National Highway Traffic Safety Administration. (2016b). *Fatality Analysis Reporting System (FARS) Analytical User's Manual 1974-2015*. Washington, D.C.: U. S. D. o. Transportation. Retrieved from <http://www.nber.org/fars/ftp.nhtsa.dot.gov/fars/FARS-DOC/Analytical%20User%20Guide/USERGUIDE-2015.pdf>.
- Newmeyer, M. N., Swortwood, M. J., Andersson, M., Abulseoud, O. A., Scheidweiler, K. B., & Huestis, M. A. (2017a). Cannabis Edibles: Blood and Oral Fluid Cannabinoid Pharmacokinetics and Evaluation of Oral Fluid Screening Devices for Predicting Delta9-Tetrahydrocannabinol in Blood and Oral Fluid following Cannabis Brownie Administration. *Clin Chem*, 63(3), 647-662. doi:10.1373/clinchem.2016.265371.
- Newmeyer, M. N., Swortwood, M. J., Andersson, M., Abulseoud, O. A., Scheidweiler, K. B., & Huestis, M. A. (2017b). Cannabis Edibles: Blood and Oral Fluid Cannabinoid Pharmacokinetics and Evaluation of Oral Fluid Screening Devices for Predicting Delta(9)-Tetrahydrocannabinol in Blood and Oral Fluid following Cannabis Brownie Administration. *Clin Chem*, 63(3), 647-662. doi:10.1373/clinchem.2016.265371.
- Newmeyer, M. N., Swortwood, M. J., Barnes, A. J., Abulseoud, O. A., Scheidweiler, K. B., & Huestis, M. A. (2016). Free and Glucuronide Whole Blood Cannabinoids' Pharmacokinetics after Controlled Smoked, Vaporized, and Oral Cannabis Administration in Frequent and Occasional Cannabis Users: Identification of Recent Cannabis Intake. *Clin Chem*, 62(12), 1579-1592. doi:10.1373/clinchem.2016.263475.
- Quantisal™ Oral Fluid Collection Device. (2018). Retrieved from <https://www.alere.com/en/home/product-details/QuantisalOralFluidCollectionDevice-au.html>.
- Rocky Mountain High Intensity Drug Trafficking Area. (2015). *The Legalization of Marijuana in Colorado: The Impact*.
- Rogeberg, O., & Elvik, R. (2016). The effects of cannabis intoxication on motor vehicle collision revisited and revised. *Addiction*, 111(8), 1348-1359. doi:10.1111/add.13347.
- Salomonsen-Sautel, S., Min, S. J., Sakai, J. T., Thurstone, C., & Hopfer, C. (2014). Trends in fatal motor vehicle crashes before and after marijuana commercialization in Colorado. *Drug Alcohol Depend*, 140, 137-144. doi:10.1016/j.drugalcdep.2014.04.008.
- Scherer, J. N., Fiorentin, T. R., Borille, B. T., Pasa, G., Sousa, T. R. V., von Diemen, L., . . . Pechansky, F. (2017). Reliability of point-of-collection testing devices for drugs of abuse in oral fluid: A systematic review and meta-analysis. *Journal of Pharmaceutical and Biomedical Analysis*, 143, 77-85. doi:10.1016/j.jpba.2017.05.021.
- Subramanian, R. (2002). *Transitioning to multiple imputation - A New method to estimate missing blood alcohol concentration (BAC) in FARS*. Springfield, VA: National Center for

- Statistics and Analysis. Retrieved from <https://crashstats.nhtsa.dot.gov/Api/Public/ViewPublication/809403>.
- Swortwood, M. J., Newmeyer, M. N., Abulseoud, O. A., Andersson, M., Barnes, A. J., Scheidweiler, K. B., & Huestis, M. A. (2017). On-site oral fluid Delta(9)-tetrahydrocannabinol (THC) screening after controlled smoked, vaporized, and oral cannabis administration. *Forensic Toxicology*, *35*(1), 133-145. doi:10.1007/s11419-016-0348-3.
- Tefft, B. C., Arnold, L. S., & Grabowski, J. G. (2016). Prevalence of Marijuana Involvement in Fatal Crashes: Washington, 2010–2014.
- Verstraete, A., Knoche, A., Jantos, R., Skopp, G., Gjerde, H., Vindenes, V., . . . Lillsunde, P. (2011). Per se limits: methods of defining cut-off values for zero tolerance.
- Wall, M. E., Sadler, B. M., Brine, D., Taylor, H., & Perez-Reyes, M. (1983). Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. *Clin Pharmacol Ther*, *34*(3), 352-363.
- Walsh, J. M. (2008). New technology and new initiatives in US workplace testing. *Forensic Sci Int*, *174*(2-3), 120-124. doi:10.1016/j.forsciint.2007.03.011
- Walsh, J. M., Verstraete, A. G., Huestis, M. A., & Mørland, J. (2008). Guidelines for research on drugged driving. *Addiction*, *103*(8), 1258-1268.
- Wang, G. S., Roosevelt, G., Le Lait, M. C., Martinez, E. M., Bucher-Bartelson, B., Bronstein, A. C., & Heard, K. (2014). Association of unintentional pediatric exposures with decriminalization of marijuana in the United States. *Ann Emerg Med*, *63*(6), 684-689. doi:10.1016/j.annemergmed.2014.01.017.
- Westin, A. A., Mjønes, G., Burchardt, O., Fuskevåg, O. M., & Slørdal, L. (2014). Can Physical Exercise or Food Deprivation Cause Release of Fat-Stored Cannabinoids? *Basic & Clinical Pharmacology & Toxicology*, *115*(5), 467-471. doi:10.1111/bcpt.12235.
- Whitehill, J. M., Rivara, F. P., & Moreno, M. A. (2014). Marijuana-using drivers, alcohol-using drivers, and their passengers: prevalence and risk factors among underage college students. *JAMA Pediatr*, *168*(7), 618-624. doi:10.1001/jamapediatrics.2013.5300.
- Wong, A., Keats, K., Rooney, K., Hicks, C., Allsop, D. J., Arnold, J. C., & McGregor, I. S. (2014). Fasting and exercise increase plasma cannabinoid levels in THC pre-treated rats: an examination of behavioural consequences. *Psychopharmacology (Berl)*, *231*(20), 3987-3996. doi:10.1007/s00213-014-3532-3.
- Wong, A., Montebello, M. E., Norberg, M. M., Rooney, K., Lintzeris, N., Bruno, R., . . . McGregor, I. S. (2013). Exercise increases plasma THC concentrations in regular cannabis users. *Drug Alcohol Depend*, *133*(2), 763-767. doi:10.1016/j.drugalcdep.2013.07.031
- Wood, E., Brooks-Russell, A., & Drum, P. (2016). Delays in DUI blood testing: Impact on cannabis DUI assessments. *Traffic Inj Prev*, *17*(2), 105-108. doi:10.1080/15389588.2015.1052421.
- World Health Organization. (2017). Adolescent Health. Retrieved from http://www.who.int/topics/adolescent_health/en/.
- Zou, G. (2004). A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*, *159*(7), 702-706.

Chapter 2: Driving Under the Influence of Marijuana and Marijuana-Involved Motor Vehicle Crashes in Massachusetts

Introduction

Experimental research suggests that marijuana (cannabis) use impairs functions related to safe driving (Huestis, 2002). Epidemiological evidence for the increase in the magnitude of motor vehicle crash risk from marijuana use ranges from 22% to 100% (a doubling) (Asbridge et al., 2012; G. Li et al., 2017; Rogeberg & Elvik, 2016). In studies of Colorado adults (Davis et al., 2016) as well as college students (Whitehill, Rivara, & Moreno, 2014), and high school students (K. Li, Simons-Morton, Gee, & Hingson, 2016), driving under the influence of marijuana (DUI-marijuana) is common among marijuana users. These individuals, as well as passengers who ride with a driver under the influence of marijuana (RUI-marijuana), would experience any increased risk for involvement in a motor vehicle crash that exists when the driver has used marijuana.

As Massachusetts implements legal retail marijuana sales for all adults, it is important to understand the prevalence of driving under the influence of marijuana and riding with a marijuana-using driver prior to the start of retail marijuana sales for non-medical use among adults age 21 and over. These topics are not well-measured in other Massachusetts datasets that have been previously collected for other purposes. Such information will be necessary to measure the extent to which there are changes in the prevalence of these events after retail adult-use marijuana sales are implemented. Another useful “baseline” measure related to marijuana and motor vehicle crashes is how frequently crash-involved drivers test positive for marijuana. Although such testing does not indicate that the driver was intoxicated by or impaired by marijuana at the time of the crash, such data nonetheless provides some information on information relevant to maintaining safe roadways, such as the extent to which drivers are tested for cannabinoids and cannabinoid disposition among drivers.

This chapter describes two studies related to driving and marijuana use. First, we present an analysis of data from the statewide population survey conducted as part of the MBHS that addresses DUI-marijuana and RUI-marijuana. Second, we present an analysis of Massachusetts data from the Fatality Analysis Reporting System which includes information on fatal crashes (i.e. crashes in which one occupant died within 30 days of the crash) and the state’s Crash Data System which includes information on all crashes on Massachusetts roadways.

Methods

Population survey of Massachusetts adults

We conducted a population-based, mail and Internet survey of Massachusetts residents age 18 years and older. This study was approved by the Institutional Review Board at the Massachusetts Department of Public Health. A copy of the survey instrument can be found in Appendix A. Details on the methods of survey design, data collection, measures, and statistical procedures, including survey weighting, can be found in Task 1, Chapter 2 of this Marijuana Baseline Health Study report. In addition to the measures

described therein, several questions were added to the survey for the purpose of addressing DUI-marijuana and RUI-marijuana.

Measures

DUI-marijuana was assessed with the item “During the past 30 days, how many times have you driven a car or other motor vehicle while you were under the influence of marijuana?” Response options included 0 times, 1 time, 2-3 times, 4-5 times, or 6 or more times. RUI-marijuana was ascertained with the question “During the past 30 days, how many times did you ride as a passenger in a car or other motor vehicle when the driver was under the influence of marijuana” with the same response options as listed above.

Parallel questions were asked for alcohol and other substances. We also asked about driving after the concurrent use of multiple substances with response options that included: marijuana and alcohol, marijuana and other drugs, alcohol and other drugs, or marijuana, alcohol, and other drugs.

Statistical analysis

Please see the methods section in Chapter 2, Task 1 for details on weighting and statistical procedures for this survey. As noted therein, a total of 3,268 non-duplicate survey questionnaires were returned with 212 determined ineligible. After screening for completion and eligibility, there were a total of 3,023 eligible surveys. The logic-checking process resulted in identification of 1 case in which multiple questions had unreasonable responses. This case was dropped, resulting in a final analytic sample of 3,022.

Several variables relevant to this chapter were re-coded from the original data. DUI-marijuana was dichotomized as a yes/no variable indicating any driving under the influence of marijuana in the past 30 days. RUI-marijuana was similarly dichotomized. Frequency of marijuana use in the past 30 days was categorized as a 3-level variable (0 days, 1-20 days, 21 or more days). Frequency of alcohol use, originally measured in days per week, was categorized as a 3-level variable (0 days, 1-4 days, 5-7 days).

First, we examined bivariate differences in driving under the influence of substances and riding with a substance-using driver between adults who had used marijuana in the past 30 days and those who had not. Next, we examined bivariate differences in socio-demographics and substance use behavior by DUI-marijuana and RUI-marijuana status. Differences were tested with chi-squared tests for categorical variables. Finally, to assess which factors were associated with DUI-marijuana and RUI-marijuana, we estimated relative risk (RR) using Poisson regression with robust standard errors (Zou, 2004). We examined associations between driving under the influence of marijuana (yes/no) and age, gender, race/ethnicity, education, frequent marijuana use, alcohol use, and riding under the influence of marijuana. When variables were not significant in initial models they were not retained in the final model, with the exception of age, gender, and race, and alcohol use. We used a similar multivariable regression approach with RUI-marijuana as the dependent variable. We used a two-tailed significance level

at $p < 0.05$ for all statistical tests. All analyses were weighted and were conducted using commands that accounted for the complex survey design, yielding results that are adjusted to be representative of the adult population in Massachusetts. The analysis for this report was generated using SAS/STAT software, Version 9.4 of the SAS System for Windows (Copyright © 2016 SAS Institute Inc. Cary, NC, USA.) with the exception of the regression models which were generated using Stata 15 statistical software (StataCorp, LLC, College Station, TX).

Fatality Analysis Reporting System (FARS)

To estimate the prevalence of marijuana, alcohol and other drug use by drivers in fatal crashes, 11 years of data (2006-2016) from the Fatality Analysis Reporting System (FARS) were studied. FARS is a national database maintained by the states and administered by the National Highway Traffic Safety Administration (NHTSA). It contains detailed information on every person and vehicle involved in a fatal crash in 26 linkable datasets. The various datasets are compiled at the state level; a state FARS analyst coordinates with the various agencies to gather the necessary data. For example, the police will provide information on the crash (manner of collision, time, location, etc.) and the medical examiner will provide toxicology information (blood alcohol content, presence of drugs, etc.).

For this analysis, two FARS datasets were utilized, the “Person” and “Accident” files. The “Person” file contains an entry for each individual involved in a fatal crash whether they are the driver, a passenger, or a non-motorist. This dataset contains information such as demographics, seating position, drug and alcohol test results. The “Accident” file contains crash level information such as time and location of the crash, manner of collision and overall number of fatalities. A full list of fields and datasets can be found in the FARS Analytical User’s Manual (National Highway Traffic Safety Administration, 2016).

Measures

From the FARS “Accident” dataset only the field reflecting the number of fatalities resulting from the crash (FATALS) was used. All other variables came from the FARS “Person” dataset, which included an indicator of “person type” which denotes whether the person was a driver, passenger or non-motorist (PER_TYP). We used an indicator of injury severity to identify individuals who died in a crash.

Demographic measures

The FARS fields for the person’s age, sex, and race/ethnicity were included in this analysis. Within FARS, race is only coded for deceased persons. There are 18 options for race and an additional six options that indicate whether the person was of Hispanic/Latino descent. The available categories were condensed into five categories: White, non-Hispanic; Black, non-Hispanic; Asian, non-Hispanic; Other, non-Hispanic; and any Hispanic/Latino.

Cannabis and other drug measures

FARS includes information on the type of drug testing conducted stored in three variables (DRUGTST1/ DRUGTST2/ DRUGTST3). Persons involved in a fatal crash can have up to three types of drug tests (e.g. blood, urine, etc.) recorded in FARS in these fields. Also included are up to three results from the reported drug tests (DRUGRES1/ DRUGRES2/ DRUGRES3). The DRUGRES fields report a code to indicate the specific drugs detected, although the level of drug concentrations are not available within the dataset. There are over 600 different drug types and an exhaustive list can be found in the 2016 FARS/CRSS Coding and Validation Manual (National Highway Traffic Safety Administration, 2016).

This analysis focused upon cannabinoids which are indicated in FARS with the following codes:

- 600 – Delta 9
- 601 – Hashish Oils
- 602 – Hashish
- 603 – Marijuana/Marihuana
- 604 – Marinol
- 605 – Tetrahydrocannabinols (THC)
- 695 – Cannabinoid, Type Unknown

A summary variable was created to indicate whether a drug test result was positive for any of the seven cannabinoid codes listed above. Delta-9-THC is a primary psychoactive compound from the cannabis plant that contributes to the ‘high’ that users experience. As described in Chapter 1, it is metabolized in the body into other cannabinoids that can be detected in laboratory testing but are not necessarily psychoactive. Generally, delta-9-THC is measurable in blood for a shorter duration after marijuana use than other metabolites, but this is complicated by individual characteristics such as frequency of cannabis use. Prior studies of marijuana involvement in crashes using FARS data in other states tend to focus on delta-9-THC because it is associated with the effects of cannabis (Tefft et al., 2016). However, it is important to note that driver *impairment* in the crash cannot be discerned from values of delta-9-THC or other compounds. Delta-9-THC, when present, is generally indicative of recent marijuana use.

Two years of FARS data (2011 and 2012) appeared anomalous in that there were near-zero levels of code 600 indicating a positive test for Delta-9-THC among drivers given a blood test for drugs. This was inconsistent with other years of Massachusetts FARS data in this analysis and inconsistent with published reports of FARS data from other states (Grondel, Hoff, & Doane, 2018). This absence of code 600 for delta-9-THC in two years of FARS data is likely to be a result of data collection or data entry practices and not indicative of true rates. Additionally, in the 11 years of Massachusetts data, there were only two recorded cases of a person testing positive for codes 601, 602, 603, or 604. In light of these potential irregularities in the cannabis codes observed in FARS, we

report on the presence of “any cannabinoid” which, though less specific than the code for delta-9-THC, appeared more reliable.

Alcohol measures

The presence of alcohol in a person is recorded in two fields within the FARS database. ATST_TYP reports the type of alcohol test given (blood, breath, etc.) and ALC_RES indicates the results of alcohol testing such as the blood alcohol content obtained from the given alcohol test. Due to problems that arise from missing data, blood alcohol content (BAC), estimates of alcohol-impaired driving are typically reported after NHTSA uses a multiple imputation process for cases in which testing was not conducted or reported (Subramanian, 2002). Imputation was not used in the present study for alcohol because the focus was on marijuana-involved crashes. NHTSA does not presently have a standardized imputation procedure for cannabis-related test results, although such procedures are being developed and tested with promising results (Chen, Williams, Liu, Chihuri, & Li, 2018). To facilitate comparison across substances within this report, only known BAC values were used in this analysis. The estimates in this report for fatalities with alcohol involvement, therefore, may not match the publicly available estimates which incorporate imputed BAC values.

Analysis

The total number of fatal crashes, number of fatally-injured persons, number of fatal crash-involved drivers, and number of deceased drivers were tabulated. Numbers and percentages of drivers who received a blood test for alcohol or drugs were calculated and graphed, as appropriate. Numbers and proportions of drivers testing positive for any cannabinoid, by driver sex, race/ethnicity, and age, and the extent to which cannabinoids were found in conjunction with alcohol, and with other drugs were calculated.

Crash Data System (CDS)

In addition to FARS, the Massachusetts Crash Data System (CDS) was utilized to examine trends in frequency of marijuana-related crashes. Unlike FARS, CDS contains every reported motor vehicle crash, and not just crashes with a fatality. However, CDS is based on the Massachusetts crash report form which is completed by the police officer who responded to the crash. This crash report form does not contain the same level of detail as FARS; it does not contain any fields related to known or suspected drug use.

As an alternative to a specific drug use field, the crash narrative was utilized. The crash narrative is a free form field where the responding officer can include any information they felt to be important that couldn't be captured within the existing crash report fields. A query was written which identified crash reports which had a crash narrative containing the keywords “marijuana”, “weed”, and “cannabis”. The keywords “high” and

“pot” were originally queried as well but these resulted in a high rate of false positives so they were excluded from the final query.

While it is not possible to determine how many non-fatal crashes occurred which involved marijuana, the aforementioned method provides insight into the number of crashes in which the responding officer suspected marijuana involvement.

Results

Population survey of Massachusetts adults

Sample Characteristics

The demographic patterns of survey respondents by reported marijuana use in the past 30 days are provided in Table 1. In reporting survey results, all estimates are weighted and all percentages represent population estimates.

Table 1. Select sample demographics. Reproduced from Task 1, Chapter 2, Table 1

	Used marijuana in past 30 days			Did not use marijuana in past 30 days			Total		
	n=439 (21.1%)			n=2583 (76.4%)					
	Weighted %	95% CI		Weighted %	95% CI		Weighted %	95% CI	
Gender									
Female	42.3	35.6	48.9	55.5	52.7	58.4	52.7	50.0	55.4
Male	57.7	51.1	64.4	44.5	41.6	47.3	47.3	44.6	50.0
Age									
18-20	9.6*	4.2	15.0	2.2	0.8	3.6	3.8*	2.1	5.4
21-25	14.7	9.5	20.0	4.2	2.5	5.8	6.4	4.7	8.1
26-29	14.3	9.1	19.6	7.4	5.5	9.2	8.9	7.0	10.7
30-39	18.1	13.1	23.2	16.8	14.4	19.1	17.0	14.9	19.2
40-49	15.5	10.0	20.9	17.6	15.2	19.9	17.1	15.0	19.3
50=59	15.3	11.8	18.9	18.0	16.1	19.9	17.5	15.8	19.1
60-69	10.1	7.2	13.1	16.7	15.0	18.4	15.3	13.8	16.8
>=70	2.3	0.6*	3.9	17.2	15.5	18.9	14.0	12.6	15.4
Education									
High school or less	38.4	31.1	45.7	31.9	28.8	34.9	33.2	30.4	36.1
College	53.1	46.1	60.1	48.8	45.9	51.6	49.7	47.0	52.4
Graduate school	8.5	6.1	10.9	19.4	17.6	21.1	17.1	15.5	18.6
Ethnicity									
Hispanic	12.0	7.0	16.9	8.7	6.4	10.9	9.4	7.3	11.4
White, non-Hispanic	70.8	64.0	77.7	75.4	72.6	78.3	74.5	71.8	77.1
Black, non-Hispanic	7.1*	2.7	11.6	5.5	4.0	7.0	5.8	4.3	7.4
Asian, non-Hispanic	3.2*	0.7	5.7	7.3	5.6	9.0	6.4	5.0	7.8
Other, non-Hispanic	6.9	3.1	10.7	3.1	2.1	4.1	3.9	2.8	5.0
Region									
Boston	13.8	9.0	18.6	14.3	12.1	16.4	14.2	12.2	16.2
Central	13.3	9.1	17.5	14.6	12.7	16.4	14.3	12.6	16.0
Metrowest	18.3	12.6	24.0	22.1	19.8	24.5	21.3	19.1	23.6
Northeast	17.4	12.3	22.4	18.4	16.2	20.7	18.2	16.1	20.3
Southeast	18.8	12.9	24.6	18.9	16.7	21.1	18.9	16.8	21.0
Western	18.5	13.7	23.3	11.6	10.0	13.3	13.1	11.4	14.7

Note: * denotes fewer than 25 respondents; table reproduced from Task 1, Chapter 2.

Prevalence of driving under the influence and riding with a substance-using driver

Among the estimated 21.1% of the adult population that used marijuana, the prevalence of driving under the influence of marijuana in the past 30 days was 34.3% (Table 2). Overall, 7.2% of the adult population drove under the influence of marijuana in the past 30 days. For assessment of RUI-marijuana, both non-users and users of marijuana were considered to have engaged in the behavior if they reported riding as a passenger

with a driver that is under the influence of marijuana. Results show that 11.3% of Massachusetts adults rode with a marijuana-using driver in the past 30 days. The proportion who RUI-marijuana was statistically significantly higher among marijuana users (36.7%) compared to non-users (4.2%) [$p < 0.001$].

We found that 6.9% of the population drove under the influence of alcohol (DUI-alcohol) and 7.9% of all adults rode as a passenger with a driver under the influence of alcohol (Table 2). Marijuana users were more likely to report DUI-alcohol (15.2%) compared to non-users (4.7%) ($p < 0.001$) and to report RUI-alcohol (14.6%) compared to non-users (6.1%) ($p < 0.001$).

Subpopulation prevalence

By age, we found that 25.6% of young adults age 18-20 years reported driving under the influence of marijuana, and 24.1% of those age 21-25 years. The proportion of adults in each age group who drove after marijuana use subsequently drops off among older age groups. (Table 3). Among females, 5.5% reported DUI-marijuana, which was statistically significantly less than the percentage of males reporting DUI-marijuana (9.1%) ($p = 0.04$).

We observed that as the number of days per month of marijuana use increases, the proportion of individuals who drive under the influence of marijuana also increases. Among individuals who use marijuana 21 days per month or more, just over 50% reported DUI-marijuana.

By age, we also found that nearly 36% of 18-20 year old adults reported riding with a marijuana-using driver in the past 30 days. Prevalence was 38% among those age 21-25 years, then lower for older age groups (Table 3). We did not observe a difference by gender or race/ethnicity. Prevalence of RUI-marijuana was lowest among those with a post-graduate degree (5.7%).

A higher proportion of those who drove under the influence of marijuana reported riding as a passenger with marijuana-using driver (67.5%) compared to marijuana users who did not drive under its influence (21.2%) ($p < 0.001$) (Table 4). We found that 42.8% of individuals who drove under the influence of marijuana reported driving under the influence of alcohol and marijuana, used simultaneously

Table 2. Prevalence of driving under the influence of alcohol, marijuana, or other substances and riding with a substance-using driver, Massachusetts adults, 2017

	Marijuana users n=439			Marijuana non- users n=2583			Total n=3022			P- value
	%	95% LCI	95% UCI	%	95% LCI	95% UCI	%	95% LCI	95% UCI	
Past 30-day behaviors										
Drove under the influence of marijuana	34.3	27.6	41.0	.	.	.	7.2	5.5	8.8	
Rode with driver under influence of marijuana	36.7	29.9	43.6	4.2	2.8	5.7	11.3	9.2	13.4	<0.001
Drove under the influence of alcohol	15.2	10.3	20.2	4.7	3.4	5.9	6.9	5.5	8.4	<0.001
Rode with a driver under influence of alcohol	14.6	10.1	19.1	6.1	4.9	7.3	7.9	6.5	9.3	<0.001
Drove under the influence of other substances	0.9	0.1	1.7	0.5	0.1	1.0	0.6	0.2	1.0	0.440
Rode with a driver under the influence of other substances	2.3	0.7	3.9	1.1	0.4	1.9	1.4	0.7	2.0	0.205
Drove under influence of any substance	37.2	30.4	44.0	5.0	3.7	6.3	11.8	9.9	13.8	<0.001
Rode with driver under the influence of any substance	42.2	35.2	49.2	10.2	8.4	12.0	17.0	14.8	19.3	<0.001

Table 3. Past 30-day prevalence of DUI-marijuana and RUI-marijuana, by demographic group

	Drove under the influence of marijuana				Rode with a driver who was under the influence of marijuana			
	%	95% LCL	95% UCL	p-value	%	95% LCL	95% UCL	p-value
Overall	7.2	5.5	8.8		11.3	9.2	13.4	
Age								
18-20	25.6*	5.5	45.6	0.002	35.8	14.2	57.5	<0.001
21-25	24.1	12.3	35.8		38.0	24.5	51.6	
26-34	11.7	6.8	16.5		18.1	12.0	24.3	
35-64	4.5	3.0	6.0		7.7	5.6	9.7	
65+	1.1	0.3	1.9		1.4	0.5	2.4	
Gender								0.600
Female	5.5	3.6	7.5	0.042	11.9	9.1	14.7	
Male	9.1	6.3	11.8		10.8	7.7	13.9	
Ethnicity								
Any Hispanic	11.5	3.5	19.6	0.139	18.4	8.8	28.0	0.390
White, non-Hispanic	6.9	5.1	8.7		10.3	8.1	12.4	
Black, non-Hispanic	1.9*	0.0	4.3		15.0	2.7	27.4	
Asian, non-Hispanic	3.5*	0.0	7.5		8.3	2.0	14.6	
Other, non-Hispanic	16.2	2.9	29.4		13.5	0.5	26.6	
Education								0.027
High school or less	7.0	3.4	10.5	0.009	11.4	6.9	15.9	
College	9.4	7.0	11.7		13.5	10.7	16.4	
Graduate school	2.2	0.8	3.5		5.7	3.3	8.1	
# days using marijuana, past 30 days								0.032
1-5 days	17.9	9.6	26.1		21.2	11.9	30.4	
6-10 days	17.8	2.8	32.7		36.9	15.4	58.5	
11-15 days	45.4	21.2	69.6		52.9	28.3	77.5	
16-20 days	47.1	21.6	72.5		45.3	19.5	71.2	
21 or more days	53.6	41.7	65.4		49.4	37.4	61.4	

* Based on small cell size of 5 or fewer. Percentages are row percents.

Characteristics of individuals who drive under the influence of marijuana (DUI-marijuana)

Table 4 also shows characteristics and substance use behaviors of marijuana users who drove under the influence of marijuana compared to those who did not. We found no differences in the distribution of gender or ethnicity by DUI-marijuana status. Of those who drove under the influence of marijuana, 47.1% did so six or more times in the

past 30 days, 32.7% did so 2-5 times, and 17% did so just once. Of these individuals, 67.5% also rode with a driver who was under the influence of marijuana once or more in the past 30 days; 8% did so only one time.

Table 4. Demographic characteristics by driving under the influence among adult marijuana users

	Drove under the influence of marijuana n=129			Did not drive under the influence of marijuana n=302			Total marijuana users n=439			P-value
	%	95% LCI	95% UCI	%	95% LCI	95% UCI	%	95% LCI	95% UCI	
Age										
18-20	13.3*	2.3	24.4	7.8	1.9	13.8	9.7	4.2	15.2	0.185
21-25	21.3	10.9	31.7	11.6	5.6	17.5	14.9	9.6	20.3	
26-29	11.9	5.1	18.7	15.9	8.6	23.2	14.5	9.2	19.9	
30-39	23.0	12.5	33.5	16.0	10.5	21.4	18.4	13.2	23.5	
40-49	12.2	4.0	20.4	17.2	10.1	24.4	15.5	10.0	21.0	
50=59	11.7	6.6	16.7	17.4	12.6	22.2	15.5	11.8	19.1	
60-69	5.7	2.6	8.9	12.4	8.2	16.6	10.1	7.1	13.1	
>=70	0.9*	0.0	1.8	1.6	0.7	2.6	1.4	0.7	2.1	
Gender										
Female	40.5	28.7	52.3	42.6	34.4	50.8	41.9	35.2	48.6	0.771
Male	59.5	47.7	71.3	57.4	49.2	65.6	58.1	51.4	64.8	
Ethnicity										
Any Hispanic	15.1	4.9	25.3	10.6	5.1	16.1	12.1	7.1	17.2	0.277
White, non-Hispanic	71.5	59.6	83.3	71.1	62.7	79.6	71.2	64.4	78.1	
Black, non-Hispanic	1.6*	0.0	3.5	10.1	3.4	16.7	7.1	2.6	11.7	
Asian, non-Hispanic	3.0*	0.0	6.6	2.1*	0.0	4.7	2.5	0.4	4.5	
Other, non-Hispanic	8.8	1.0	16.6	6.1	1.8	10.4	7.0	3.1	10.9	
Frequency of DUI Marijuana										
0 times	.	.	.	100.0	100.0	100.0	65.7	59.0	72.4	
once	17.0	8.9	25.2	.	.	.	5.9	2.9	8.8	
2-3 times	30.0	18.3	41.8	.	.	.	10.3	5.6	15.0	
4-5 times	2.7	0.7	4.7	.	.	.	0.9	0.3	1.6	
6 or more	47.1	34.9	59.3	.	.	.	16.2	10.8	21.5	
yes, frequency unknown	3.1*	0.0	6.1	.	.	.	1.0	0.0	2.1	
Rode with driver under influence of marijuana	67.5	56.4	78.6	21.2	13.6	28.7	37.1	30.2	44.1	<0.001

Frequency of RUI-Marijuana										
0 times	32.5	21.4	43.6	78.8	71.3	86.4	62.9	55.9	69.8	<0.001
once	8.0	3.2	12.9	7.6	3.4	11.8	7.8	4.5	11.0	
2-3 times	30.2	18.2	42.3	8.5	2.1	14.9	16.0	9.9	22.1	
4-5 times	6.2	0.4	12.1	3.2	0.4	6.1	4.3	1.5	7.0	
6 or more	23.0	12.8	33.2	1.8	0.5	3.2	9.1	5.2	13.0	
DUI- alcohol	46.8	33.8	59.8	3.7	1.4	6.0	18.8	12.9	24.8	<0.001
RUI -alcohol	19.3	11.0	27.5	12.5	7.0	18.0	14.8	10.2	19.4	0.175
DUI- combined alcohol and marijuana	42.8	27.7	57.9	.	.	.	16.0	9.0	23.1	-

Note: Table displays column percentages. DUI=Drove under the influence; RUI-marijuana=Rode as a passenger with a driver under the influence.*based on ≤25 responses

Among those who used both marijuana and alcohol in the past 30 days, 46.8% of those who drove under the influence of marijuana also drove under the influence of alcohol. In comparison, users of both marijuana and alcohol who did not drive under the influence of marijuana had a much lower prevalence of driving under the influence of alcohol, at only 3.7%.

Characteristics of individuals who ride with driver under the influence of marijuana (RUI-marijuana)

Table 5 shows a comparison of demographic and substance use characteristics between individuals who rode with a driver under the influence of marijuana and those who did not. The distribution of RUI-marijuana by age showed that higher proportions of younger individuals tended to engage in this behavior versus older individuals. . Most individuals (70.6%) who RUI-marijuana had used marijuana in the past 30 days; this is in contrast to 15.5% of individuals who did not RUI-marijuana who reported past-30 day marijuana use.

Factors associated with driving under the influence of marijuana (DUI-marijuana) and riding with a driver under the influence of marijuana (RUI-marijuana)

Our multivariable Poisson regression model (Table 6) with DUI-marijuana as the outcome included age, gender, race/ethnicity, frequent marijuana use and alcohol use (Table 6). In preliminary models, we found no association between education level and DUIM and dropped it from subsequent models. We found that Black, non-Hispanic individuals had an 81% lower risk of DUI-marijuana compared to White, non-Hispanics (RR=0.19; 95% CI:0.05-0.75). Frequent marijuana use (defined as using on 21 or more days in the past month) was associated with a 63% increased risk of DUI-marijuana compared to using on 20 days or fewer (RR=1.63; 95% CI:1.15-2.32). Of the model covariates, riding with a marijuana-using driver demonstrated the strongest association with DUI-marijuana. Individuals who rode with a driver under the influence of marijuana had more than triple the risk of DUI-marijuana compared to marijuana users who did not ride with a marijuana-using driver (RR=3.42; 95% CI: 2.28-5.15).

Table 5. Demographic and substance use characteristics by riding under the influence among MA adults

	Rode under the influence of marijuana			Did not ride under the influence of marijuana			Total respondents			P-value
	n=187			n=2720			n=3022			
	%	95% LCI	95% UCI	%	95% LCI	95% UCI	%	95% LCI	95% UCI	
Age										
18-20	12.2	3.7	20.8	2.8	1.3	4.3	3.9	2.2	5.6	<0.001
21-25	20.8	12.7	29.0	4.4	2.8	5.9	6.2	4.5	7.9	
26-29	15.5	7.6	23.4	8.1	6.2	10.0	9.0	7.1	10.9	
30-39	24.2	15.7	32.6	16.2	13.9	18.4	17.1	14.9	19.3	
40-49	11.5	5.5	17.6	18.1	15.7	20.5	17.4	15.1	19.6	
50-59	9.8	6.2	13.4	18.1	16.3	20.0	17.2	15.5	18.9	
60-69	4.6	2.2	6.9	16.7	15.0	18.4	15.3	13.8	16.8	
>=70	1.4	0.2	2.6	15.6	14.0	17.2	14.0	12.6	15.4	
Gender										
Female	55.1	45.1	65.1	52.4	49.5	55.2	52.7	49.9	55.4	0.599
Male	44.9	34.9	54.9	47.6	44.8	50.5	47.3	44.6	50.1	
Ethnicity										
Any Hispanic	15.2	7.2	23.1	8.6	6.4	10.7	9.3	7.2	11.4	0.389
White, non-Hispanic	67.5	57.4	77.6	75.1	72.3	78.0	74.3	71.5	77.0	
Black, non-Hispanic	7.8	1.0	14.7	5.7	4.1	7.2	5.9	4.3	7.5	
Asian, non-Hispanic	4.8	1.1	8.6	6.8	5.3	8.4	6.6	5.1	8.1	
Other, non-Hispanic	4.7	0.0	9.5	3.8	2.7	4.9	3.9	2.7	5.0	
Education										
High school or less	33.5	22.9	44.1	33.7	30.7	36.8	33.7	30.8	36.7	0.027
College	58.1	47.8	68.4	48.2	45.4	51.0	49.3	46.6	52.1	
Graduate school	8.3	4.6	12.1	18.1	16.4	19.7	16.9	15.4	18.5	
Used marijuana	70.6	61.9	79.3	15.5	13.2	17.8	21.7	19.2	24.3	<0.001
Drove under influence of marijuana	44.2	34.2	54.1	2.7	1.6	3.8	7.4	5.7	9.1	<0.001
Frequency of RUIIM										
0 times	-	-	-	-	-	-	88.7	86.6	90.8	
once	26.5	18.2	34.8	-	-	-	3.0	2.0	4.0	
2-3 times	43.9	33.7	54.0	-	-	-	5.0	3.4	6.5	
4-5 times	10.5	4.9	16.1	-	-	-	1.2	0.5	1.8	
6 or more	19.2	11.9	26.5	-	-	-	2.2	1.3	3.0	

Drove under the influence of alcohol	18.1	10.7	25.5	5.5	4.1	6.8	6.9	5.4	8.4	0.001
Rode with driver under influence of alcohol	25.2	17.0	33.4	5.4	4.4	6.5	7.7	6.3	9.0	<0.001

Note: Table displays column percentages.

Table 6. Adjusted relative risk for driving under the influence of marijuana

	Adjusted Relative Risk	95% Confidence Limits		P-value
Age 25 and older (ref: 18-24 years)	1.02	0.72	1.43	0.911
Male (ref: Female)	1.32	0.96	1.82	0.089
Hispanic (ref: White, non-Hispanic)	1.22	0.76	1.97	0.404
Black (ref: White, non-Hispanic)	0.19	0.05	0.75	0.018
Asian (ref: White, non-Hispanic)	1.10	0.53	2.26	0.797
Other (ref: White, non-Hispanic)	1.30	0.60	2.83	0.507
≥21 days of marijuana use (Ref: ≤20 days)	1.63	1.15	2.32	0.007
Used alcohol	1.35	0.80	2.28	0.256
Rode with driver under influence of marijuana	3.42	2.28	5.15	<.0001

Note: Results from multivariable, modified Poisson regression. Only marijuana users included. All substance use and DUI or RUI variables refer to behavior in the past 30 days

Our multivariable Poisson regression model with RUI-marijuana as the outcome included age, gender, education, race/ethnicity, frequent marijuana use, alcohol use, and riding as a passenger with driver under the influence of alcohol (RUI-alcohol) (Table 7). We found that being age 25 years or older was associated with a nearly 50% reduction in the risk of RUI-marijuana, controlling for other factors. Using marijuana between 1-20 days per month was associated with having more than 5 times the risk of RUI-marijuana (RR=5.79; 95% CI: 3.70-9.07) compared to not using at all; using 21 or more days per month increased the risk more than 8 times (RR=8.57; 95% CI: 5.42-13.55). Riding with a driver who used alcohol was associated with more than twice the risk of riding with a marijuana using driver.

Table 7. Adjusted relative risk for riding as a passenger with a driver under the influence of marijuana

	Adjusted Relative Risk	95% Confidence Limits		P-value
Age 25 and older (ref: 18-24 years)	0.52	0.37	0.74	<.0001
Male (ref: Female)	0.76	0.55	1.05	0.098
College education (ref: ≤ High School)	1.04	0.69	1.56	0.865
Graduate education (ref: ≤ High School)	0.82	0.47	1.43	0.49
Hispanic (ref: White, non-Hispanic)	1.26	0.73	2.15	0.409
Black (ref: White, non-Hispanic)	1.24	0.65	2.39	0.512
Asian (ref: White, non-Hispanic)	1.35	0.63	2.90	0.441
Other (ref: White, non-Hispanic)	0.87	0.38	1.99	0.735
1 - 20 days of marijuana use (Ref: 0 days)	5.79	3.70	9.07	<.0001
≥21 days of marijuana use (Ref: 0 days)	8.57	5.42	13.55	<.0001
Used alcohol	0.97	0.62	1.53	0.907
Rode with a driver under influence of alcohol	2.25	1.66	3.05	<.0001

Note: Results from multivariable, modified Poisson regression. Entire sample (marijuana users and non-users) included. All substance use and DUI or RUI variables refer to behavior in the past 30 days

Fatality Analysis Reporting System (FARS)

From 2006-2016, there were an average of 373 traffic fatalities per year. 2015 had the lowest number of traffic deaths since 2009, 345, but in 2016 this number increased to 389, the highest number since 2007 when there were 434 traffic-related fatalities (Figure 1, Table 8).

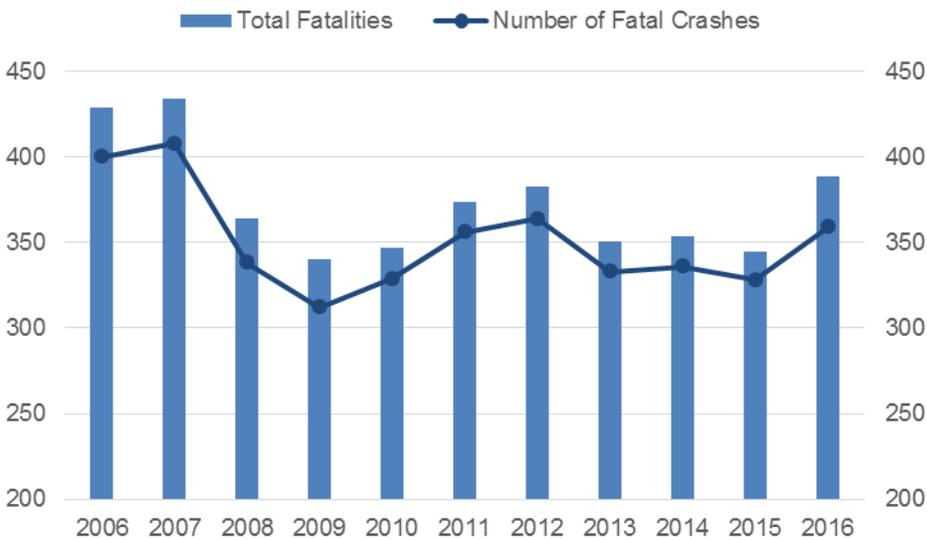


Figure 1. Total fatalities and number of motor vehicle crashes with a fatality in Massachusetts by year (2006-2016)

Table 8. Number of fatal crashes and total number of fatalities in Massachusetts, 2006-2016

Year	Number of Fatal Crashes	Traffic Fatalities in MA	Number of Drivers Involved in a Fatal Crash	Number of Deceased Drivers
2006	403	429	568	284
2007	408	434	570	277
2008	338	364	442	218
2009	313	340	447	216
2010	330	347	448	220
2011	356	374	499	239
2012	365	383	497	225
2013	334	351	445	212
2014	336	354	456	212
2015	328	345	457	210
2016	359	389	501	234

The number of drivers involved in a fatal crash followed a similar trend to the number of fatalities per year (Table 8, Figure 2.) Overall, there were an average of 484 drivers involved in a fatal crash each year from 2006 to 2016 and an average of 231 drivers were deceased from motor vehicle crashes.

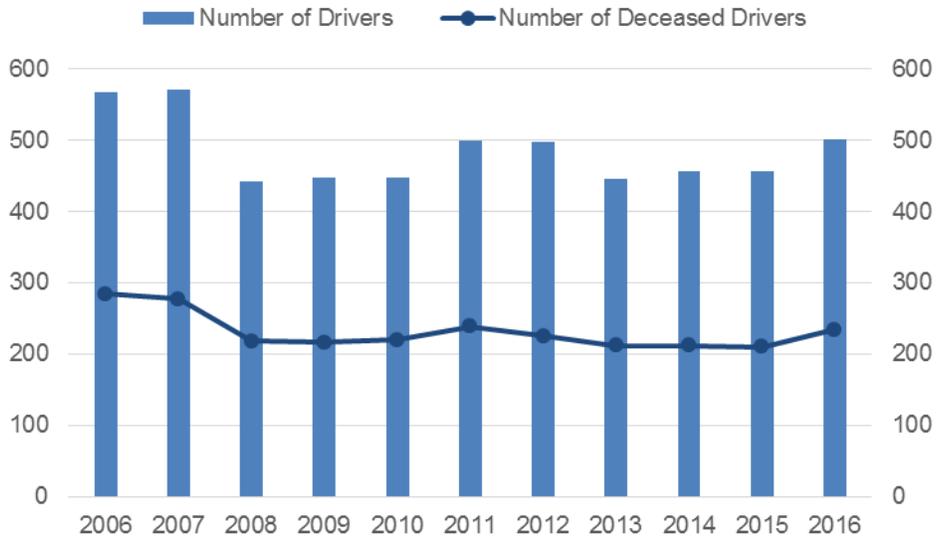


Figure 2. Number of drivers involved in fatal crashes and number of deceased drivers in MA by year (2006-2016)

Toxicological Testing

When drivers in a fatal crash are given a blood test, it is indicated in FARS under the ATST_TYP (alcohol test type) and DRUGTST (drug test type) fields. There were three

instances in the 11-year sample where a driver was given a blood test for drugs but not for alcohol, and 54 instances of the reverse, when a driver's blood was tested for alcohol but not drugs. Nearly 1900 drivers had their blood tested for both drugs and alcohol after a fatal crash in the 11-year sample, out of 5330 total crash-involved drivers, which is approximately 36% (Table 9.).

Table 9. Blood test types for drivers involved in fatal crashes in MA (2006-2016)

Year	Alcohol Test Only	Drug Test Only	Alcohol and Drug Test	Total Drivers	Percent tested for alcohol and drugs
2006	3	1	215	568	37.9
2007	9	0	207	570	36.3
2008	16	0	156	442	35.3
2009	9	0	155	447	34.7
2010	2	0	186	448	41.5
2011	3	1	149	499	29.9
2012	1	0	172	497	34.6
2013	1	0	164	445	36.9
2014	4	0	142	456	31.1
2015	6	0	159	457	34.8
2016	0	1	192	501	38.3
Total	54	3	1897	5330	35.6

Within the FARS database there are three options that can be selected to indicate that a person was tested for the presence of drugs: (1) blood test, (2) urine test, and (3) both blood and urine tests. Among these three options, for both surviving and deceased drivers, blood tests were used, almost exclusively, to determine the presence of drugs. In the 11-year sample, 1897 drivers were given only a blood test, three were given a urine test only and only one person was given both a blood and urine test to determine if drugs were present in their system after being involved in a fatal crash.

Overall, approximately 73% of the drivers who were deceased in a crash were given a post-mortem blood test for alcohol or drugs. By contrast, less than 1% of drivers who survived a crash in which there was at least one fatality were given a blood test for alcohol or drugs according to the FARS data (Figure 3). During the 11-year study period (2006-2016), the highest proportion of deceased drivers given a blood test for alcohol or drugs was 83% in 2010 and the lowest was 63% in 2011. The highest proportion of surviving drivers given a blood test for alcohol or drugs was 2% in 2005 and the lowest was 0% in 2009 and 2015. In 2016, the proportion of deceased drivers given a blood test for alcohol or drugs was 82%, which was a slightly higher testing rate for deceased drivers than in the preceding five years, and less than 1% of surviving drivers were tested.

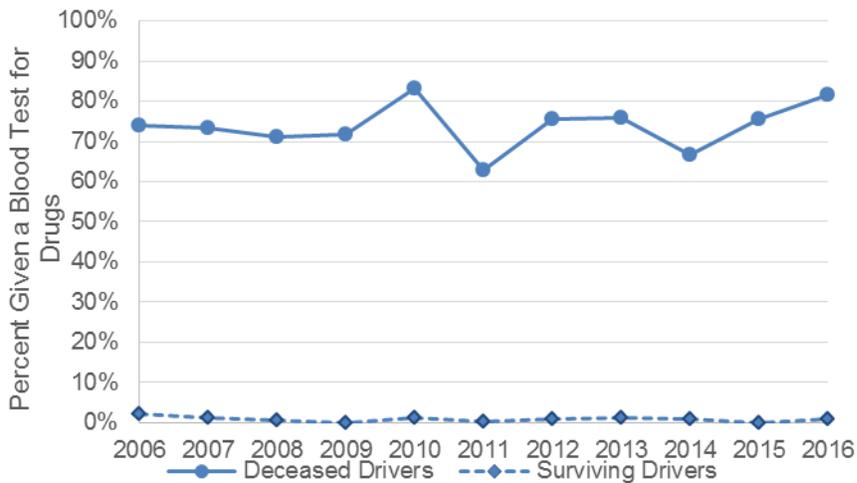


Figure 3. Percentage of deceased and surviving drivers in fatal crashes given a Blood test for drugs

To detect potential demographic differences in blood-testing trends, testing rates were examined by race/ethnicity. Figure 4 displays the percent of all deceased drivers who were given a blood test by race/ethnicity. The “Other, non-Hispanic” category was lower than others, due to this category containing the “Unknown” race option which was strongly correlated with having an “unknown drug test type.”

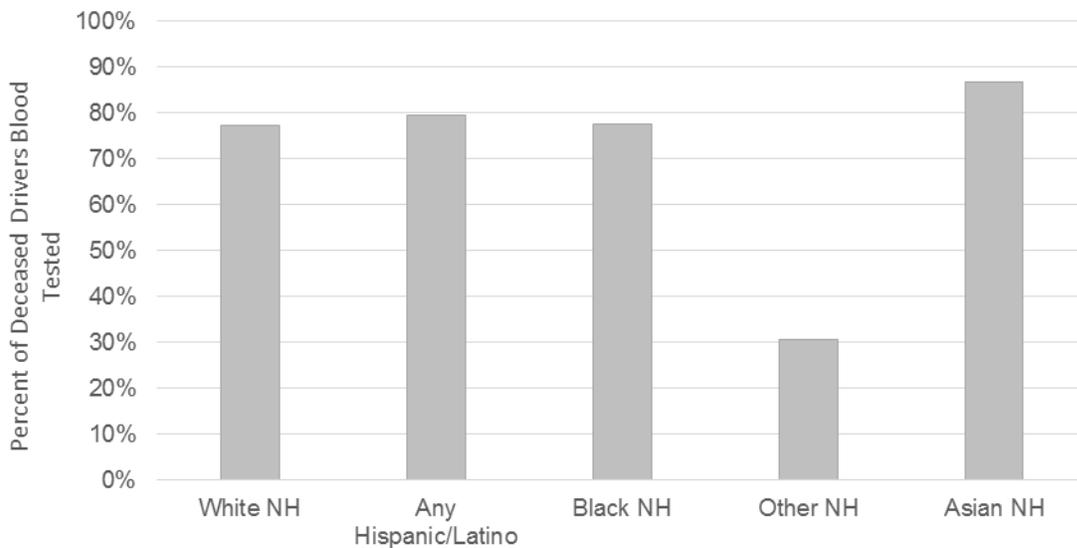


Figure 4. Percent of deceased drivers given a blood test for drugs, by race/ethnicity.

Marijuana Use

The prevalence of marijuana use among deceased drivers blood-tested for drugs was evaluated by examining how often they tested positive for any cannabinoid (Figure 5).

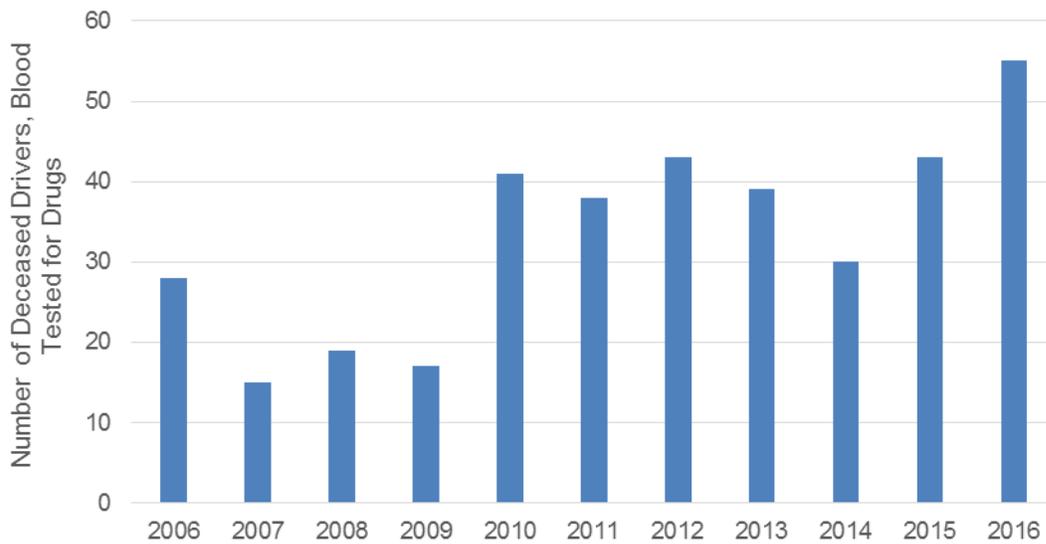


Figure 5. Number of deceased drivers given a blood test for drugs testing positive for any cannabinoid

When examining the frequency in which deceased drivers given a blood test for drugs tested positive for any cannabinoid, a noticeable increase was observed in 2010 (Figure 6).

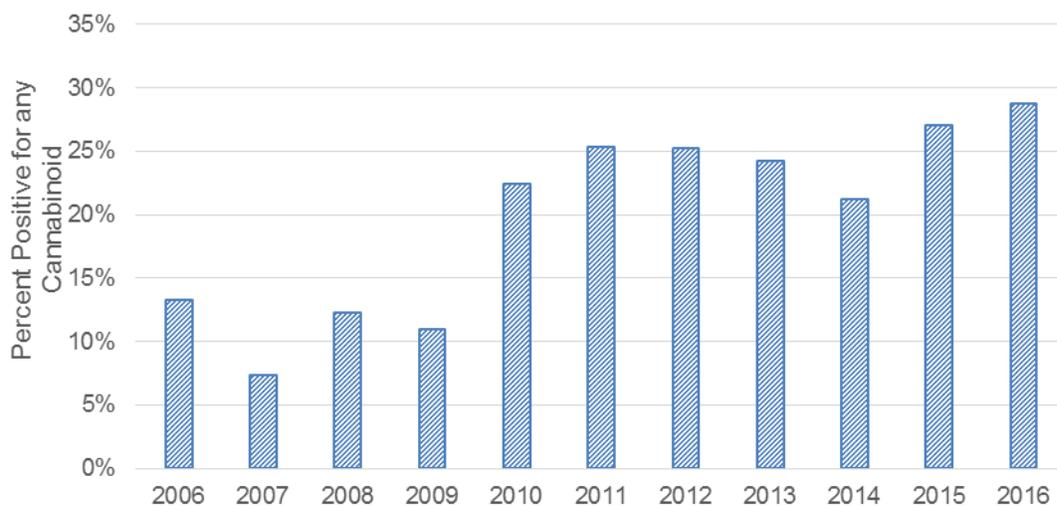


Figure 6. Percentage of deceased drivers given a blood test for drugs who tested positive for any cannabinoid

The data was further examined by driver sex, race, and age in order to identify potential differences in marijuana use in these demographic groups (Table 10).

Table 10. Number of deceased drivers given a blood test for drugs who tested positive for any cannabinoid by sex, race, and age

Demographic Category	Any Cannabinoid		No Cannabinoids		Total
	n	%	n	%	
Male	297	20.3%	1167	79.7%	1464
Female	71	17.1%	343	82.9%	414
White, non-Hispanic	275	17.8%	1272	82.2%	1547
Black, non-Hispanic	42	34.4%	80	65.6%	122
Asian, non-Hispanic	1	7.7%	12	92.3%	13
Other, non-Hispanic	12	18.8%	52	81.3%	64
Any Hispanic/Latino	38	28.8%	94	71.2%	132
<18 years	12	26.1%	34	73.9%	46
18-20 years	47	32.9%	96	67.1%	143
21-25 years	115	33.0%	233	67.0%	348
26-34 years	87	27.4%	231	72.6%	318
35-64 years	99	13.3%	644	86.7%	743
65+ years	8	2.9%	272	97.1%	280

Note: Rows percentages are reported. Any cannabinoid + no cannabinoid will sum to 100% within demographic groups.

When examining cannabinoid presence, there was no statistically significant difference between male and female drivers (Figure 7).

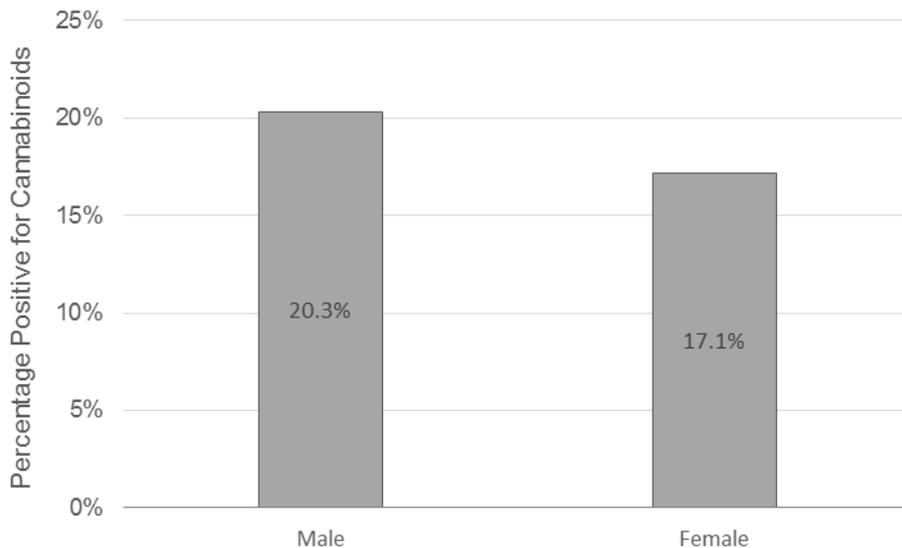


Figure 7. Percentage of deceased drivers given a blood test for drugs who tested positive for any cannabinoid, by driver sex

When examining race/ethnicity of deceased drivers given a blood test for drugs, the proportion of individuals of any Hispanic/Latino ethnicity and Black, non-Hispanic race/ethnicity who tested positive for cannabinoids was higher than for White, non-Hispanic drivers (Figure 8). There were very small samples of deceased Asian, non-Hispanic and Other, non-Hispanic drivers.

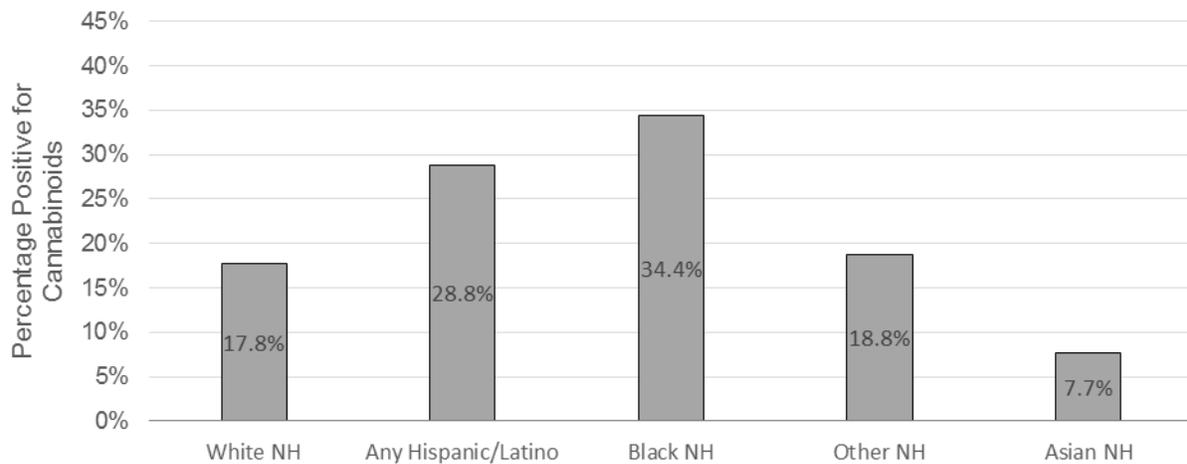


Figure 8. Percentage of all deceased drivers given a blood test for drugs who tested positive for any cannabinoid, by driver race/ethnicity

Figure note: NH=non-Hispanic

The presence of any cannabinoid in deceased drivers given a blood test for drugs was most common in young drivers and decreased precipitously from the 26-34 age group to the 35-64 age group, as shown in Figure 9.

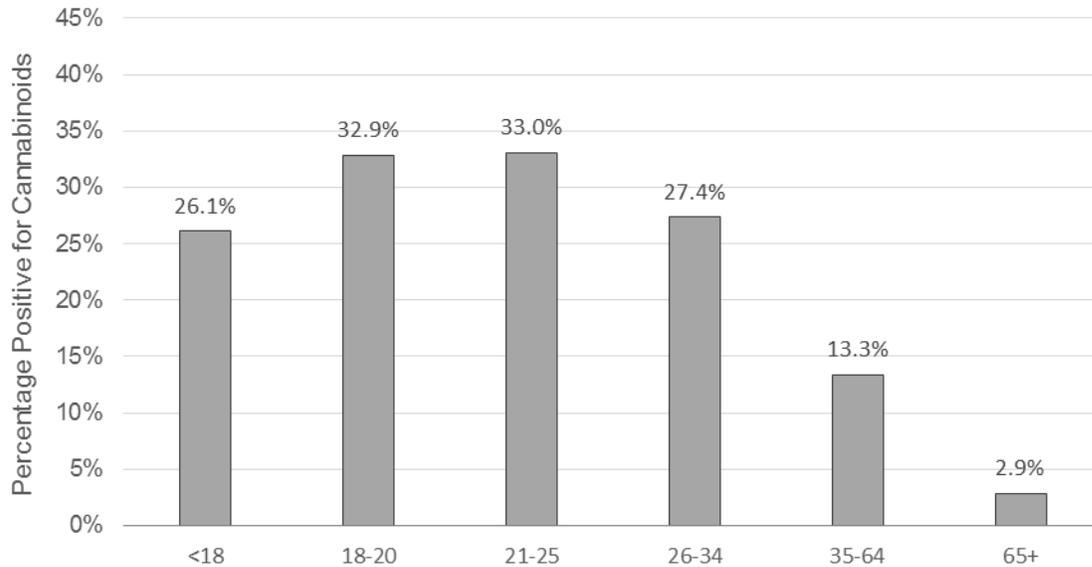


Figure 9. Percentage of deceased drivers given a blood for drugs who tested positive for any cannabinoid by driver age

Alcohol and Drug Use

Reducing the prevalence of drunk driving has long been a focal point for the public health community as a way to reduce motor vehicle crash injuries and deaths. As such, the presence of alcohol in fatal crashes was examined, both by itself and in conjunction with the presence of cannabinoids (Table 11). For all demographic categories, with the exception of Black, non-Hispanics there were more blood-tested, deceased drivers with a blood alcohol content greater than or equal to 0.08% than with cannabinoids in their system.

Cannabinoid results were examined in conjunction with alcohol use. Table 11 displays the number of deceased drivers given a blood test for drugs and alcohol who tested positive for any cannabinoid only, had a BAC \geq 0.08% only, had both a positive cannabinoid result and a BAC \geq 0.08% or tested negative for cannabinoids and had a BAC less than 0.08%.

Table 11. Number of deceased drivers given a blood test for alcohol and drugs who tested positive for any cannabinoid and/or had a blood alcohol content (BAC) \geq 0.08% by sex, race/ethnicity, and age.

Demographic Category	Any Cannabinoid, BAC \leq 0.08%		No Cannabinoid, BAC \geq 0.08%		Any Cannabinoid + BAC \geq 0.08%		No Cannabinoid, BAC \leq 0.08%		Total
	n	%	n	%	n	%	n	%	
Male	176	12.0%	383	26.2%	119	8.1%	752	51.4%	1464
Female	33	8.0%	86	20.8%	38	9.2%	245	59.2%	414
White, non-Hispanic	151	9.8%	395	25.5%	124	8.0%	840	54.3%	1547
Any Hispanic/Latino	29	22.0%	33	25.0%	9	6.8%	57	43.2%	132
Black, non-Hispanic	21	17.2%	21	17.2%	19	15.6%	57	46.7%	122
Other, non-Hispanic	8	12.5%	17	26.6%	4	6.3%	34	53.1%	64
Asian, non-Hispanic	0	0.0%	3	23.1%	1	7.7%	9	69.2%	13
<18 years	8	17.4%	7	15.2%	4	8.7%	26	56.5%	46
18-20 years	29	20.3%	31	21.7%	17	11.9%	62	43.4%	143
21-25 years	61	17.5%	103	29.6%	54	15.5%	126	36.2%	348
26-34 years	46	14.5%	104	32.7%	40	12.6%	119	37.4%	318
35-64 years	59	7.9%	206	27.7%	40	5.4%	418	56.3%	743
65+ years	6	2.1%	18	6.4%	2	0.7%	246	87.9%	280

Table Note: Other drugs could be present in any column. A small portion (2.4%) of all deceased drivers given a blood test for alcohol and drugs had an unknown alcohol result and are excluded from the table.

When examining alcohol and cannabis presence in fatal crash-involved drivers by age group, a trend emerges. The proportion of drivers that had only a BAC \geq 0.08% increased with age until peaking in the 26-34 years age category, whereas those with only a positive cannabinoid result peaked in the 18-20 years age group and then declined with age (Figure 10). As expected from these two trends, having both a positive cannabinoid result and a BAC \geq 0.08% peaked in the 21-25 years age group.

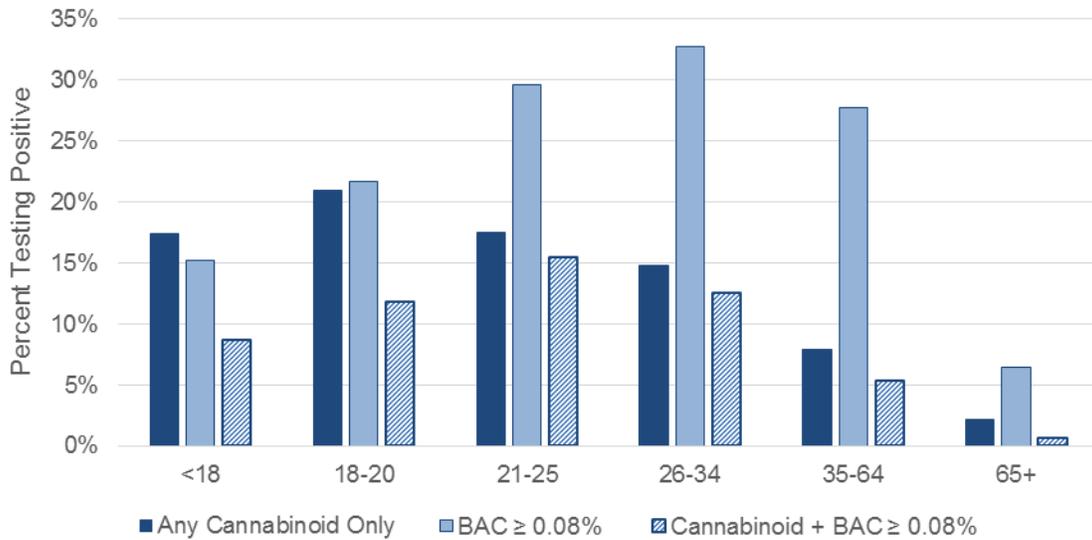


Figure 10. Percentage of all deceased drivers given a blood test for alcohol and drugs who tested positive for any cannabinoid and/or had a blood alcohol content (BAC) ≥ 0.08%, by driver age (years).

The trend in drivers with a BAC ≥ 0.08% and/or positive cannabinoid results was examined over time (Figure 11.) In 2007 and 2008, nearly 40% of all deceased drivers given a blood test for alcohol and drugs had a BAC ≥ 0.08%.

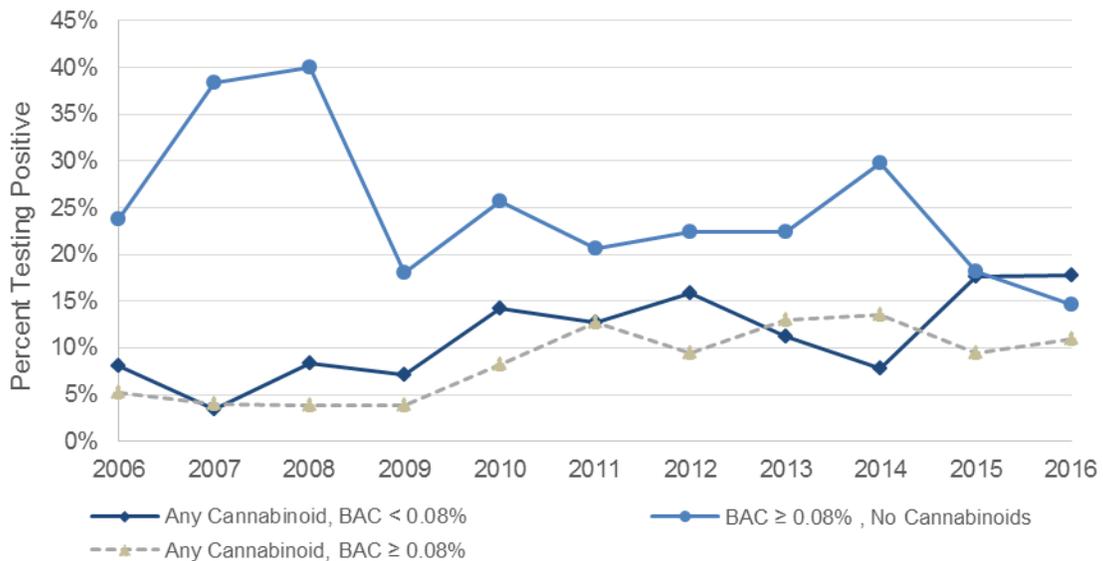


Figure 11. Percentage of all deceased drivers given a blood test for alcohol and drugs who tested positive for any cannabinoid and/or had a BAC ≥ 0.08% in Massachusetts from 2006 to 2016

The number of deaths resulting from these crashes has followed a similar trend (Figure 12). While the number of deaths from drivers with a BAC $\geq 0.08\%$ and no cannabinoids in their blood has steadily decreased since 2006, the number of deaths from drivers with cannabinoids and with a BAC below the legal limit of 0.08%, has steadily increased.

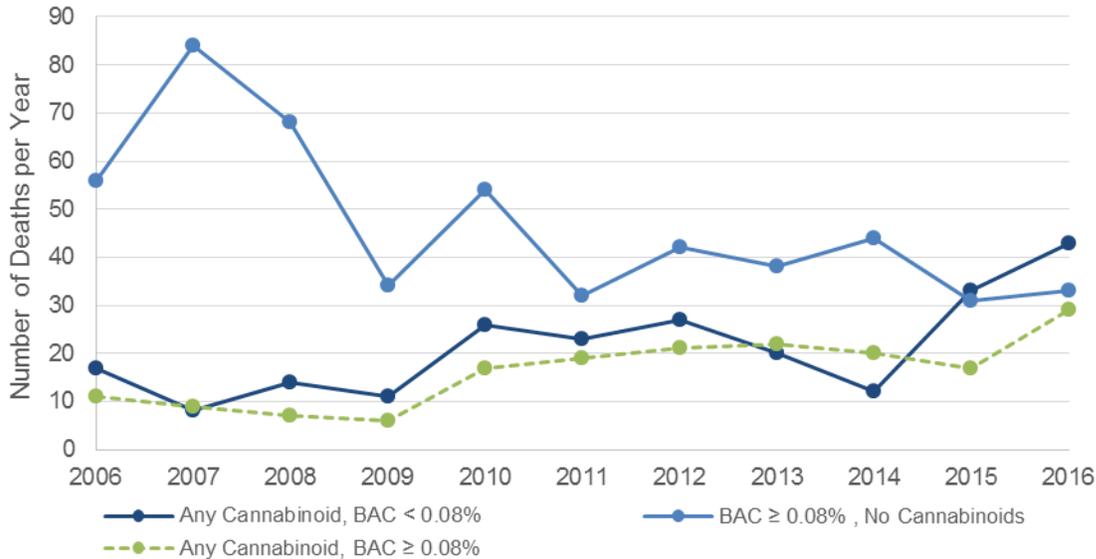


Figure 12. Number of deaths per year resulting from crashes with deceased drivers given a blood test for alcohol and drugs who tested positive for any cannabinoid and/or had a BAC $\geq 0.08\%$ in Massachusetts from 2006 to 2016.

The presence of other drugs was examined in addition to alcohol and cannabinoids. Figure 13 shows the frequency at which other drugs were present in blood-tested, deceased drivers. The drug categories were taken from the 2016 FARS/NASS GES Coding and Validation Manual (National Highway Traffic Safety Administration, 2016) with “Other” encompassing all drugs other than cannabinoids, narcotics, stimulants, depressants, and hallucinogens/PCP. Overall, all drug categories have generally trended upwards in the past 11 years.

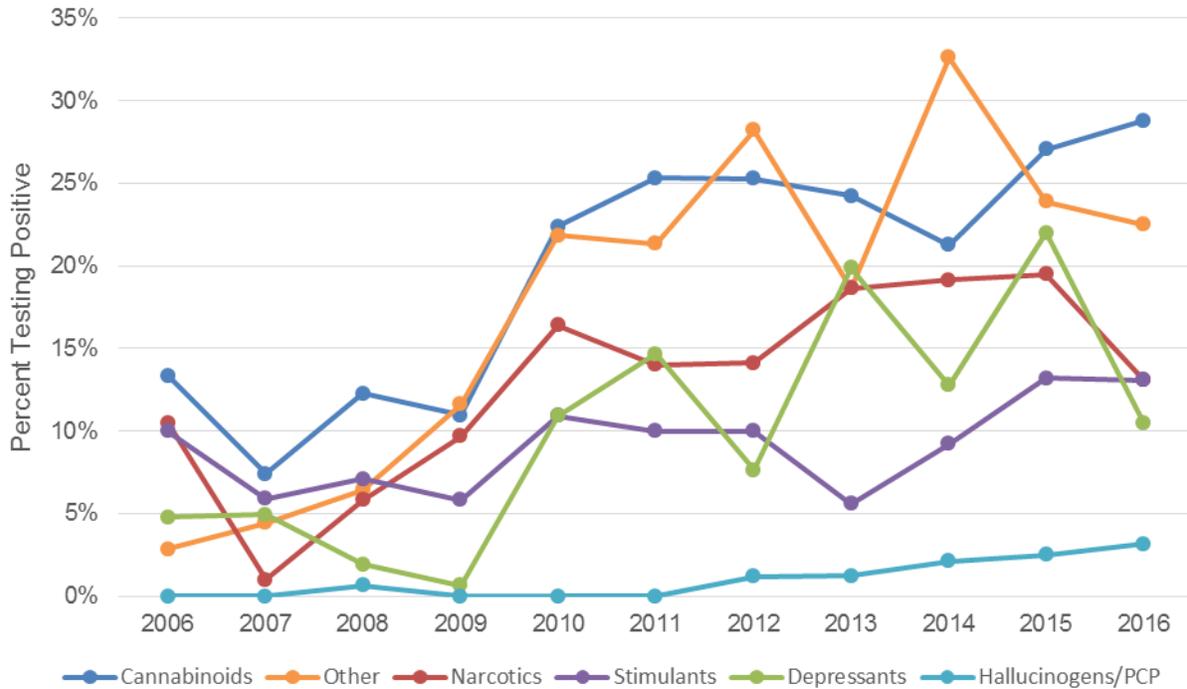


Figure 13. Percentage of all deceased, drivers given a blood test for drugs who tested positive for various drug categories in Massachusetts from 2006 to 2016.

Figure note: Totals will not sum to 100% as drivers could test positive in multiple categories. Cases with a positive test result but unknown drug type are excluded (0.2% of drivers given a blood test for drugs).

Drugs besides cannabinoids were analyzed in conjunction with alcohol (BAC ≥ 0.08) and any cannabinoids (Table 12). When examining racial/ethnic differences, White, non-Hispanic drivers were more likely to have only other drugs in their system than cannabinoids (Table 13). The same did not hold true for drivers with any Hispanic/Latino ethnicity and Black, non-Hispanic drivers. Those groups were equally or more likely to have cannabinoids only in their system than other drugs only. Sample sizes were too small for the other racial/ethnic categories to make similar comparisons.

Table 12, Table 13 and Table 14 show the number and frequency of deceased drivers by sex, race and age (respectively) testing positive for the seven combinations of cannabinoids, drugs and alcohol (defined as a BAC $\geq 0.08\%$) or none of those results.. Females were less likely than males to have a blood alcohol content above the legal limit or test positive for cannabinoids only, but were more likely than males to have a positive result for only other drugs (Table 12).

Table 12. Number and proportion of deceased drivers given a blood test for drugs who tested positive for any cannabinoid and/or had a blood alcohol content (BAC) \geq 0.08% and/or positive results for other drugs, by driver sex

Type	Male		Female	
	n	%	n	%
Cannabinoids Only (MJ)	98	6.7%	12	2.9%
BAC \geq 0.08%	270	18.4%	53	12.8%
Other Drugs Only (Drugs)	261	17.8%	110	26.6%
MJ + BAC \geq 0.08%	65	4.4%	23	5.6%
MJ + Drugs	80	5.5%	21	5.1%
BAC \geq 0.08% + Drugs	113	7.7%	33	8.0%
MJ + BAC \geq 0.08% + Drugs	54	3.7%	15	3.6%
None	523	35.7%	147	35.5%
Total	1464	100%	414	100%

Table 13. Number of deceased drivers given a blood test who tested positive for any cannabinoid and/or a BAC \geq 0.08 and/or other drugs by driver race/ethnicity

Type	White NH		Hispanic/Latino		Black NH		Other NH		Asian NH	
	n	%	n	%	n	%	n	%	n	%
Cannabinoids Only (MJ)	73	4.7%	17	12.9%	17	13.9%	3	4.7%	0	0.0%
BAC \geq 0.08%	267	17.3%	27	20.5%	15	12.3%	12	18.8%	2	15.4%
Other Drugs Only (Drugs)	333	21.5%	10	7.6%	16	13.1%	11	17.2%	1	7.7%
MJ + BAC \geq 0.08%	71	4.6%	4	3.0%	11	9.0%	2	3.1%	0	0.0%
MJ + Drugs	78	5.0%	12	9.1%	6	4.9%	5	7.8%	0	0.0%
BAC \geq 0.08% + Drugs	128	8.3%	6	4.5%	6	4.9%	5	7.8%	1	7.7%
MJ + BAC \geq 0.08% + Drugs	53	3.4%	5	3.8%	8	6.6%	2	3.1%	1	7.7%
None	544	35.2%	51	38.6%	43	35.2%	24	37.5%	8	61.5%

Table Note: NH= Non-Hispanic

Examining results for alcohol, marijuana, and other drugs by age, the percentage of deceased drivers within an age group testing positive for other drugs increases with age and is highest for the 65+ age bracket (Tables 14a and 14b). Deceased blood-tested drivers in this age range rarely tested positive for cannabinoids or had a BAC above 0.08%, but frequently tested positive for other drugs (Table 14b). This is likely due to the number of medications taken by older individuals that are reported in FARS drug results.

Table 14a and 14b. Number and proportion of deceased drivers given a blood test Testing Positive for Any Cannabinoid and/or a blood alcohol content (BAC) \geq 0.08 and/or other drugs by driver age

Type	<18		18-20		21-25	
	n	%	n	%	n	%
Cannabinoids Only (MJ)	7	15.2%	17	11.9%	31	8.9%
BAC \geq 0.08% Only	6	13.0%	24	16.8%	79	22.7%
Other Drugs Only (Drugs)	6	13.0%	13	9.1%	36	10.3%
MJ + BAC \geq 0.08%	3	6.5%	11	7.7%	29	8.3%
MJ + Drugs	1	2.2%	13	9.1%	30	8.6%
BAC \geq 0.08% + Drugs	1	2.2%	7	4.9%	24	6.9%
MJ + BAC \geq 0.08% + Drugs	1	2.2%	6	4.2%	25	7.2%
None	21	45.7%	52	36.4%	94	27.0%
Total	46	100%	143	100%	348	100%

Type	26-34		35-64		65+	
	n	%	n	%	n	%
Cannabinoids Only (MJ)	24	7.5%	30	4.0%	1	0.4%
BAC \geq 0.08% Only	76	23.9%	127	17.1%	11	3.9%
Other Drugs Only (Drugs)	47	14.8%	174	23.4%	95	33.9%
MJ + BAC \geq 0.08%	20	6.3%	24	3.2%	1	0.4%
MJ + Drugs	23	7.2%	29	3.9%	5	1.8%
BAC \geq 0.08% + Drugs	28	8.8%	79	10.6%	7	2.5%
MJ + BAC \geq 0.08% + Drugs	20	6.3%	16	2.2%	1	0.4%
None	80	25.2%	264	35.5%	159	56.8%
Total	318	100%	743	100%	280	100%

Crash Data System (CDS)

The results from our query of non-fatal crash data to identify officer-written crash narratives which contained the words “marijuana”, “weed”, and “cannabis” are shown in Figure 14. This figure displays the number of non-fatal crashes per year with a crash narrative containing one or more of these keywords. Data from 2017 was included because it was available from CDS. The number of crashes per year where the responding officer suspected marijuana-involvement has followed the same increasing trend as has fatal crashes (Figure 14).

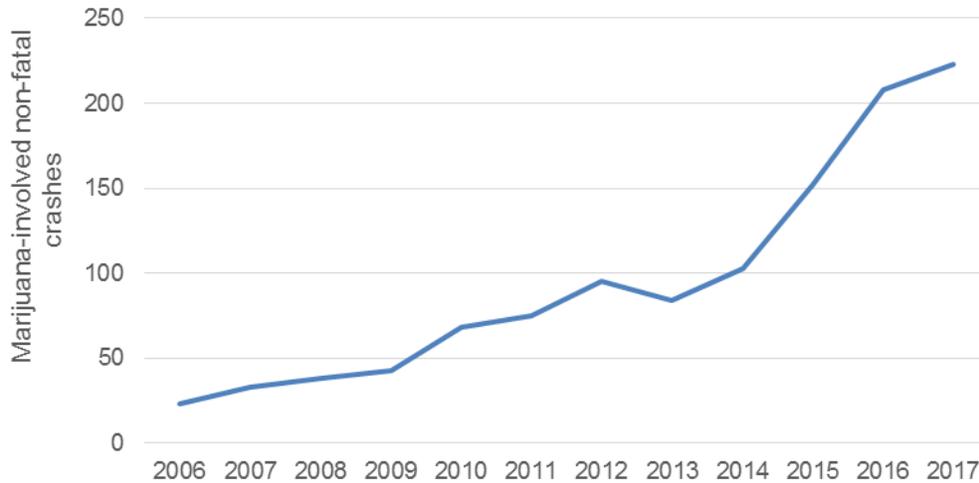


Figure 14. Non-fatal motor vehicle crashes which contain a crash narrative containing the keywords “marijuana”, “weed”, and/or “cannabis,” by year

Discussion

In 2017, 7.2% of Massachusetts adults drove under the influence of marijuana (DUI) and 11.7% rode with a driver who was under the influence of marijuana (RUI). Among marijuana users, nearly 4 in 10 reported DUI and or RUI-marijuana. When stratified by age, younger age groups appeared more likely to engage in both behaviors. We found that DUI-marijuana was reported by 25.6% of individuals age 18-20 years and 24.1% of those age 21-24 years. RUI-marijuana was reported by 36% of those age 18-20 years and 38% of those age 21-25 years. Prevalence was much lower for both DUI-marijuana and RUI-marijuana among adults age 25 years and older compared to those age 24 years and younger.

Compared to estimates from other states, the prevalence in Massachusetts of DUI- and RUI-marijuana appear higher, especially when stratified by age. However, some aspects of our results are consistent with prior work. For example, prior estimates from Colorado published in 2016 show that 6% of young adults age 18-25 years reported driving after using marijuana, while 4.8% 26-34 years old reported the behavior. Thus, our point estimates among Massachusetts adults are more than four times higher than estimates from Colorado (Department of Health and Environment). The results across states, however, are consistent in finding that prevalence of DUI-marijuana among older age groups is lower compared to younger age groups. Cross-state differences in results may be due to several factors, including regional beliefs, attitudes and policies related to DUI-marijuana.

Some prior studies have found that males are over-represented among those who drive under the influence of marijuana (Arria, Caldeira, Vincent, Garnier-Dykstra, & O'Grady, 2011; Whitehill et al., 2014). In the present study, this was not the case, with females

representing about 42% of marijuana users, and a similar proportion of those who DUI-marijuana.

About 4 out of 10 Massachusetts adults who drove under the influence of marijuana reported driving under the influence of alcohol and marijuana, simultaneously. This is concerning, since studies suggest that the crash risk from the combination of alcohol and marijuana may be higher than the risk from using either substance alone (Chihuri, Li, & Chen, 2017). Monitoring and preventing driving under the combination of alcohol and marijuana is an important consideration as legalization is implemented.

The analysis of data from fatal crashes in Massachusetts demonstrated that there were approximately 360 crashes in 2016 in which at least one person died, with a total of nearly 390 fatalities, of which 234 were drivers. Many of these crashes are preventable and reducing potentially-impairing alcohol and drug use by drivers should remain a priority as marijuana policies are changing within the state. Among the fatal crashes, approximately 36% of drivers received a blood drug test between 2002-2016. This included testing 73% of fatally injured drivers, and less than 1% of surviving drivers. To contextualize these numbers, prior studies seeking to establish national or cross-state comparisons using FARS data only include states in which testing rates are above 80% for deceased drivers. Thus, comparisons to other states may not be appropriate due to lower-than-ideal testing rates in Massachusetts.

We observed a trend that may indicate an increasing proportion of deceased drivers involved in fatal motor vehicle crashes testing positive for cannabinoids. This does not mean the drivers were impaired by marijuana at the time of the crash, and could merely indicate increasing population-level marijuana use, which would be consistent with the results from the adult survey. The analysis of FARS data showed a decrease over time in the number of deaths per year resulting from crashes with drivers who had a blood alcohol content above 0.08%, but an increase in the number of deaths with drivers testing positive for cannabinoids or a blood alcohol content above 0.08% plus cannabinoids. This trend is something that warrants future investigation in alternate data sources with regard to the possibility of either substitution (i.e. drivers using marijuana instead of alcohol) or combination (e.g. drivers using alcohol and marijuana) effects.

Limitations

As with all studies, these data are subject to several limitations. As reported in Task 1, Chapter 2, the survey response rate was 21.7%. Although this rate is in line with surveys of this kind, there is a possibility for response bias on a measure not accounted for by the weighting, which would impact generalizability. For example, if adults who did not use marijuana discarded the survey but those who used marijuana were more likely to return it, this could lead to overestimation of the prevalence of marijuana use, and related measures like driving under the influence. As marijuana legalization continues to be implemented in the Commonwealth, it will be important to replicate this survey as well as expand data collection to additional modalities that will provide a robust picture of marijuana use and related behaviors.

The cross-sectional survey design precludes determining the temporal sequencing of experiences and prevents drawing of causal inferences. Marijuana and other substance use were both self-reported, and not corroborated by testing of biological samples. Social desirability bias can lead to underestimates in survey research, however a unique contribution of this study is that it is the first to be conducted in Massachusetts after legalization of marijuana for adult recreational use. Data was collected in late 2017, nearly one year after marijuana became legal for recreational use by adults, and several years after legalization of medical marijuana in Massachusetts. This should reduce potential for social desirability bias that leads to under-reporting of marijuana use. Illegal behaviors (e.g. use of illicit drugs; driving under the influence of alcohol or drugs) may be underreported.

Small cell sizes for categories of some variables likely means that models including them are underpowered. For some variables, fewer than 5 respondents endorsed the items. Weighted estimates based on these few data should be interpreted carefully.

In conclusion, this study presents the first estimate of prevalence of DUI-marijuana and RUI-marijuana among Massachusetts adults after the legalization of marijuana for use by all adults over 21 years. Driving under the influence of marijuana is common among marijuana users, particularly among young adults. Riding as a passenger with a marijuana-using driver is even more common. Efforts to address social norms about driving under the influence of marijuana is one strategy that may reduce this behavior. In the meantime, more research to understand the true crash risk and methods for deterring impaired driving are needed.

Analysis of fatality data is also subject to limitations. In addition to a lower-than-ideal rate of testing, described above, prior studies have questioned the validity of drug data in FARS due to variability in drug testing practices, even within states (Berning & Smither, 2014). The data used for this study, which showed a dramatic dip to near-zero levels of recorded delta-9-THC results in 2011-2012 and precluded use of that data for this analysis likely reflects the type of testing and/or data coding problems that plague the FARS data.

References

- Alcohol and Drug Abuse Institute. (2013). What is Cannabis? Retrieved from <http://learnaboutmarijuana.org/factsheets/whatiscannabis.htm>
- Alere DDS®2 Mobile Test System: Rapid Screening for Drugs of Abuse in Oral Fluid. (2018). Retrieved from <https://www.alere.com/en/home/product-details/dds2-mobile-test-system.html#>
- Allen, K. R. (2011). Screening for drugs of abuse: which matrix, oral fluid or urine? *Annals of Clinical Biochemistry*, 48(6), 531-541.
- Arnett, J. J., & Tanner, J. L. (Eds.). (2004). *Emerging Adulthood: The Winding Road from the Late Teens through the Twenties*. New York, NY: Oxford University Press.
- Arria, A. M., Caldeira, K. M., Vincent, K. B., Garnier-Dykstra, L. M., & O'Grady, K. E. (2011). Substance-related traffic-risk behaviors among college students. *Drug Alcohol Depend*, 118(2-3), 306-312. doi:10.1016/j.drugalcdep.2011.04.012
- Asbridge, M., Hayden, J. A., & Cartwright, J. L. (2012). Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *BMJ*, 344, e536.
- Banta-Green, C., Rowhani-Rahbar, A., Ebel, B. E., Andris, L. M., & Qiu, Q. (2016). Cannabis Use among Drivers Suspected of Driving Under the Influence or Involved in Collisions: Analyses of Washington State Patrol Data.
- Berning, A., & Smither, D. (2014). *Understanding the Limitations of Drug Test Information, Reporting, and Testing Practices in Fatal Crashes*. Retrieved from Washington, D.C.:
- Blencowe, T., Pehrsson, A., & Lillsunde, P. (2010). *Analytical evaluation of oral fluid screening devices and preceding selection procedures*. Retrieved from https://www.bast.de/Druid/EN/deliverables-list/downloads/Deliverable_3_2_2.pdf?_blob=publicationFile&v=1
- Bondallaz, P., Favrat, B., Chtioui, H., Fornari, E., Maeder, P., & Giroud, C. (2016). Cannabis and its effects on driving skills. *Forensic Science International*, 268, 92-102. doi:<https://doi.org/10.1016/j.forsciint.2016.09.007>
- Bosker, W. M., & Huestis, M. A. (2009). Oral fluid testing for drugs of abuse. *Clinical chemistry*, 55(11), 1910-1931.
- Chen, Q., Williams, S. Z., Liu, Y., Chihuri, S. T., & Li, G. (2018). Multiple imputation of missing marijuana data in the Fatality Analysis Reporting System using a Bayesian multilevel model. *Accid Anal Prev*, 120, 262-269. doi:10.1016/j.aap.2018.08.021
- Chihuri, S., Li, G., & Chen, Q. (2017). Interaction of marijuana and alcohol on fatal motor vehicle crash risk: a case-control study. *Inj Epidemiol*, 4(1), 8. doi:10.1186/s40621-017-0105-z
- Compton, R. (2017). *Marijuana-Impaired Driving A Report to Congress*. Retrieved from Washington, DC:
- Davis, K. C., Allen, J., Duke, J., Nonnemaker, J., Bradfield, B., Farrelly, M. C., . . . Novak, S. (2016). Correlates of Marijuana Drugged Driving and Openness to Driving While High: Evidence from Colorado and Washington. *PLoS One*, 11(1), e0146853. doi:10.1371/journal.pone.0146853
- Department of Health and Environment, C. Adult marijuana use trends. *Monitoring trends in adult marijuana use*.
- Department of Health and Human Services. (2015). *Mandatory Guidelines for Federal Workplace Drug Testing Programs*. Retrieved from
- Dräger DrugTest® 5000: Analysis system for detecting drugs. (2018). Retrieved from https://www.draeger.com/Library/Content/drugtest_5000_pi_9041006_en.pdf
- Drummer, O. H. (2010). Forensic toxicology. *Exs*, 100, 579-603.

- Edwards, L. D., Smith, K. L., & Savage, T. (2017). Drugged Driving in Wisconsin: Oral Fluid Versus Blood. *J Anal Toxicol*, 41(6), 523-529. doi:10.1093/jat/bkx051
- Gentili, S., Solimini, R., Tittarelli, R., Mannocchi, G., & Busardo, F. P. (2016). A Study on the Reliability of an On-Site Oral Fluid Drug Test in a Recreational Context. *J Anal Methods Chem*, 2016, 1234581. doi:10.1155/2016/1234581
- Gentili, S., Solimini, R., Tittarelli, R., Mannocchi, G., & Busardò, F. P. (2016). A Study on the Reliability of an On-Site Oral Fluid Drug Test in a Recreational Context. *J Anal Methods Chem*, 2016, 1234581. doi:10.1155/2016/1234581
- Goodwin, R. S., Darwin, W. D., Chiang, C. N., Shih, M., Li, S.-H., & Huestis, M. A. (2008). Urinary elimination of 11-nor-9-carboxy-delta9-tetrahydrocannabinol in cannabis users during continuously monitored abstinence. *Journal of analytical toxicology*, 32(8), 562-569.
- Grondel, D., Hoff, S., & Doane, D. (2018). *Marijuana use, Alcohol Use, and riving in Washington State: Emerging Issues with Poly-Drug Use on Washington Roadways*. Retrieved from http://wtsc.wa.gov/wp-content/uploads/dlm_uploads/2018/05/Marijuana-and-Alcohol-Involvement-in-Fatal-Crashes-in-WA_FINAL.pdf
- Grotenhermen, F. (2003). Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*, 42(4), 327-360. doi:10.2165/00003088-200342040-00003
- Gunasekaran, N., Long, L. E., Dawson, B. L., Hansen, G. H., Richardson, D. P., Li, K. M., . . . McGregor, I. S. (2009). Reintoxication: the release of fat-stored $\Delta(9)$ -tetrahydrocannabinol (THC) into blood is enhanced by food deprivation or ACTH exposure. *British Journal of Pharmacology*, 158(5), 1330-1337. doi:10.1111/j.1476-5381.2009.00399.x
- Hartman, R. L., Anizan, S., Jang, M., Brown, T. L., Yun, K. M., Gorelick, D. A., . . . Huestis, M. A. (2015). Cannabinoid disposition in oral fluid after controlled vaporizer administration with and without alcohol. *Forensic Toxicology*, 33(2), 260-278. doi:10.1007/s11419-015-0269-6
- Hartman, R. L., Brown, T. L., Milavetz, G., Spurgin, A., Gorelick, D. A., Gaffney, G., & Huestis, M. A. (2016). Controlled vaporized cannabis, with and without alcohol: subjective effects and oral fluid-blood cannabinoid relationships. *Drug Test Anal*, 8(7), 690-701. doi:10.1002/dta.1839
- Hoffman, J. (2016). Study finds sharp increase in marijuana exposure among Colorado children. *The New York Times*. Retrieved from <https://www.nytimes.com/2016/07/26/health/marijuana-edibles-are-getting-into-colorado-childrens-hands-study-says.html>
- Hollister, L. E., Gillespie, H. K., Ohlsson, A., Lindgren, J. E., Wahlen, A., & Agurell, S. (1981). Do plasma concentrations of delta 9-tetrahydrocannabinol reflect the degree of intoxication? *J Clin Pharmacol*, 21(8-9 Suppl), 171s-177s.
- Huestis, M. A. (2002). Cannabis (Marijuana) - Effects on Human Performance and Behavior. *Forensic Sci Rev*, 14(1-2), 15-60.
- Huestis, M. A. (2007). Human Cannabinoid Pharmacokinetics. *Chemistry & biodiversity*, 4(8), 1770-1804. doi:10.1002/cbdv.200790152
- Huestis, M. A., Milman, G., Mendu, D., Lee, D., Barnes, A. J., Schwoppe, D., . . . Desrosier, N. A. (2013). *Evaluation the on-site Draeger DrugTest 5000 in occasional and chronic frequent smokers following controlled cannabis smoking*. Retrieved from http://www.icadtsinternational.com/files/documents/2013_058.pdf
- Huestis, M. A., Milman, G., Mendu, D., Lee, D., Barnes, A. J., Schwoppe, D. M., . . . Desrosiers, N. A. (2013). *Evaluation of the on-site Draeger DrugTest 5000 in occasional and chronic frequent smokers following controlled cannabis smoking*. Paper presented at the International Conference on Alcohol, Drugs and Traffic Safety (T2013), 20th, 2013, Brisbane, Queensland, Australia.

- Huestis, M. A., & Smith, M. L. (2018). Cannabinoid Markers in Biological Fluids and Tissues: Revealing Intake. *Trends Mol Med*, 24(2), 156-172. doi:10.1016/j.molmed.2017.12.006
- Kim, S. Y., Kim, H., Park, Y., Lim, J., Kim, J., Koo, S. H., & Kwon, G. C. (2017). Evaluation of an Automated Reader and Color Interpretation-Based Immunoassays for Multiplexed Drug-of-Abuse Testing in Urine. *J Anal Toxicol*, 41(5), 412-420. doi:10.1093/jat/bkx014
- Lee, D., Milman, G., Barnes, A. J., Goodwin, R. S., Hirvonen, J., & Huestis, M. A. (2011). Oral fluid cannabinoids in chronic, daily cannabis smokers during sustained, monitored abstinence. *Clinical chemistry*, 57(8), 1127-1136.
- Li, G., Chihuri, S., & Brady, J. E. (2017). Role of alcohol and marijuana use in the initiation of fatal two-vehicle crashes. *Annals of Epidemiology*, 27(5), 342-347.e341. doi:<https://doi.org/10.1016/j.annepidem.2017.05.003>
- Li, K., Simons-Morton, B., Gee, B., & Hingson, R. (2016). Marijuana-, alcohol-, and drug-impaired driving among emerging adults: Changes from high school to one-year post-high school. *J Safety Res*, 58, 15-20. doi:10.1016/j.jsr.2016.05.003
- Macdonald, S., Anglin-Bodrug, K., Mann, R. E., Erickson, P., Hathaway, A., Chipman, M., & Rylett, M. (2003). Injury risk associated with cannabis and cocaine use. *Drug Alcohol Depend*, 72(2), 99-115.
- Milburn, M. (2017). DRUID. Retrieved from <https://www.druidapp.com>
- Moore, C., Coulter, C., Uges, D., Tuyay, J., Van der Linde, S., Van Leeuwen, A., . . . Orbita Jr, J. (2011). Cannabinoids in oral fluid following passive exposure to marijuana smoke. *Forensic Science International*, 212(1-3), 227-230.
- National Highway Traffic Safety Administration. (2016). *Fatality Analysis Reporting System (FARS) Analytical User's Manual 1974-2015*. Retrieved from Washington, D.C.: <http://www.nber.org/fars/ftp.nhtsa.dot.gov/fars/FARS-DOC/Analytical%20User%20Guide/USERGUIDE-2015.pdf>
- Newmeyer, M. N., Swortwood, M. J., Andersson, M., Abulseoud, O. A., Scheidweiler, K. B., & Huestis, M. A. (2017a). Cannabis Edibles: Blood and Oral Fluid Cannabinoid Pharmacokinetics and Evaluation of Oral Fluid Screening Devices for Predicting Delta9-Tetrahydrocannabinol in Blood and Oral Fluid following Cannabis Brownie Administration. *Clin Chem*, 63(3), 647-662. doi:10.1373/clinchem.2016.265371
- Newmeyer, M. N., Swortwood, M. J., Andersson, M., Abulseoud, O. A., Scheidweiler, K. B., & Huestis, M. A. (2017b). Cannabis Edibles: Blood and Oral Fluid Cannabinoid Pharmacokinetics and Evaluation of Oral Fluid Screening Devices for Predicting Delta(9)-Tetrahydrocannabinol in Blood and Oral Fluid following Cannabis Brownie Administration. *Clinical chemistry*, 63(3), 647-662. doi:10.1373/clinchem.2016.265371
- Newmeyer, M. N., Swortwood, M. J., Barnes, A. J., Abulseoud, O. A., Scheidweiler, K. B., & Huestis, M. A. (2016). Free and Glucuronide Whole Blood Cannabinoids' Pharmacokinetics after Controlled Smoked, Vaporized, and Oral Cannabis Administration in Frequent and Occasional Cannabis Users: Identification of Recent Cannabis Intake. *Clin Chem*, 62(12), 1579-1592. doi:10.1373/clinchem.2016.263475
- Quantisal™ Oral Fluid Collection Device. (2018). Retrieved from <https://www.alere.com/en/home/product-details/QuantisalOralFluidCollectionDevice-au.html>
- Rocky Mountain High Intensity Drug Trafficking Area. (2015). *The Legalization of Marijuana in Colorado: The Impact*.
- Rogeberg, O., & Elvik, R. (2016). The effects of cannabis intoxication on motor vehicle collision revisited and revised. *Addiction*, 111(8), 1348-1359. doi:10.1111/add.13347
- Salomonsen-Sautel, S., Min, S. J., Sakai, J. T., Thurstone, C., & Hopfer, C. (2014). Trends in fatal motor vehicle crashes before and after marijuana commercialization in Colorado. *Drug Alcohol Depend*, 140, 137-144. doi:10.1016/j.drugalcdep.2014.04.008

- Scherer, J. N., Fiorentin, T. R., Borille, B. T., Pasa, G., Sousa, T. R. V., von Diemen, L., . . . Pechansky, F. (2017). Reliability of point-of-collection testing devices for drugs of abuse in oral fluid: A systematic review and meta-analysis. *Journal of Pharmaceutical and Biomedical Analysis*, *143*, 77-85. doi:10.1016/j.jpba.2017.05.021
- Subramanian, R. (2002). *Transitioning to multiple imputation - A New method to estimate missing blood alcohol concentration (BAC) in FARS*. Retrieved from Springfield, VA: <https://crashstats.nhtsa.dot.gov/Api/Public/ViewPublication/809403>
- Swortwood, M. J., Newmeyer, M. N., Abulseoud, O. A., Andersson, M., Barnes, A. J., Scheidweiler, K. B., & Huestis, M. A. (2017). On-site oral fluid Delta(9)-tetrahydrocannabinol (THC) screening after controlled smoked, vaporized, and oral cannabis administration. *Forensic Toxicology*, *35*(1), 133-145. doi:10.1007/s11419-016-0348-3
- Tefft, B. C., Arnold, L. S., & Grabowski, J. G. (2016). Prevalence of Marijuana Involvement in Fatal Crashes: Washington, 2010–2014.
- Verstraete, A., Knoche, A., Jantos, R., Skopp, G., Gjerde, H., Vindenes, V., . . . Lillsunde, P. (2011). Per se limits: methods of defining cut-off values for zero tolerance.
- Wall, M. E., Sadler, B. M., Brine, D., Taylor, H., & Perez-Reyes, M. (1983). Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. *Clin Pharmacol Ther*, *34*(3), 352-363.
- Walsh, J. M. (2008). New technology and new initiatives in US workplace testing. *Forensic Science International*, *174*(2-3), 120-124. doi:10.1016/j.forsciint.2007.03.011
- Walsh, J. M., Verstraete, A. G., Huestis, M. A., & Mørland, J. (2008). Guidelines for research on drugged driving. *Addiction*, *103*(8), 1258-1268.
- Wang, G. S., Roosevelt, G., Le Lait, M. C., Martinez, E. M., Bucher-Bartelson, B., Bronstein, A. C., & Heard, K. (2014). Association of unintentional pediatric exposures with decriminalization of marijuana in the United States. *Ann Emerg Med*, *63*(6), 684-689. doi:10.1016/j.annemergmed.2014.01.017
- Westin, A. A., Mjønes, G., Burchardt, O., Fuskevåg, O. M., & Slørdal, L. (2014). Can Physical Exercise or Food Deprivation Cause Release of Fat-Stored Cannabinoids? *Basic & Clinical Pharmacology & Toxicology*, *115*(5), 467-471. doi:10.1111/bcpt.12235
- Whitehill, J. M., Rivara, F. P., & Moreno, M. A. (2014). Marijuana-using drivers, alcohol-using drivers, and their passengers: prevalence and risk factors among underage college students. *JAMA Pediatr*, *168*(7), 618-624. doi:10.1001/jamapediatrics.2013.5300
- Wong, A., Keats, K., Rooney, K., Hicks, C., Allsop, D. J., Arnold, J. C., & McGregor, I. S. (2014). Fasting and exercise increase plasma cannabinoid levels in THC pre-treated rats: an examination of behavioural consequences. *Psychopharmacology (Berl)*, *231*(20), 3987-3996. doi:10.1007/s00213-014-3532-3
- Wong, A., Montebello, M. E., Norberg, M. M., Rooney, K., Lintzeris, N., Bruno, R., . . . McGregor, I. S. (2013). Exercise increases plasma THC concentrations in regular cannabis users. *Drug Alcohol Depend*, *133*(2), 763-767. doi:10.1016/j.drugalcdep.2013.07.031
- Wood, E., Brooks-Russell, A., & Drum, P. (2016). Delays in DUI blood testing: Impact on cannabis DUI assessments. *Traffic Inj Prev*, *17*(2), 105-108. doi:10.1080/15389588.2015.1052421
- World Health Organization. (2017). Adolescent Health. Retrieved from http://www.who.int/topics/adolescent_health/en/
- Zou, G. (2004). A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*, *159*(7), 702-706.

Chapter 3: Marijuana-Related Health System Contacts in Massachusetts

Introduction

Problems related to marijuana use may lead users to require medical care. This care seeking includes incidents in which someone seeks treatment for a cannabis use disorder, or could be related to an acute injury (e.g. from a cannabis-involved motor vehicle crash) or episode of marijuana-related illness. For this study, we brought together three sources of data to document the current several aspects of the current picture of health system contacts related to marijuana. Specifically, we sought to document the number and prevalence of (1) substance use treatment admissions for a primary diagnosis of cannabis use disorder; (2) emergency room and urgent care services due to marijuana, and (3) marijuana-related exposure calls received by the regional poison control center (PCC).

Since historical data is not available on use of emergency room and urgent care services for marijuana, we sought to obtain a 2017 point estimate. For treatment admissions and cannabis exposures (including unintentional exposure among youth 0-9) through poison control calls will capture trends associated with regulations, legislation and cultural shifts. As marijuana legalization of marijuana for adult use is implemented, these are valuable indicator that can serve as a benchmark against which future policy changes change be compared.

Methods

Treatment Episode Data

The national Substance Use and Mental Health Services Administration (SAMHSA) collects and publishes annual data episodes of substance use treatment in each U.S. This data includes information on the raw number and population adjusted number of admissions to substance abuse treatment by primary substance of abuse and by year. We compiled the number of marijuana-related treatment episodes for 2004-2014, with 2014 being the most recent year of data available. We also extracted information on alcohol, opioid, cocaine, and methamphetamine/amphetamine admissions for comparison purposes. We graphed the trend over time in population-adjusted admissions for marijuana, and the proportion of all admissions due to marijuana.

Population Survey of Massachusetts Adults

We analyzed the survey conducted as part of the MBHS included questions on seeking emergency or urgent care related to marijuana use. Briefly, we conducted a population-based, mail and Internet survey of Massachusetts residents age 18 years and older. This study was approved by the Institutional Review Board at the Massachusetts Department of Public Health. The survey instrument can be found in Appendix A.

Details on the methods of survey design, data collection, measures, and statistical procedures, including survey weighting, can be found in Task 1, Chapter 2. In addition to the measures described therein, several questions were added to the survey for the

purpose of addressing use of emergency room or urgent care services related to substance use.

For individuals who reported yes to using a particular substance (alcohol, marijuana, or other substances) in the past 30 days, the survey asked if they had utilized emergency room or urgent care services in relation to that substance within the past year.

Poison Control Center Exposure Calls

It can be difficult to distinguish, from secondary data, the intentionality of an exposure. For example, if teenagers intentionally experiment with marijuana but have adverse reactions, they may call poison control claiming unintentional exposure. Therefore, prior studies have coded all exposures under the age of 9 years as unintentional.

As restricting cases to children 9 years old and under has been utilized in previous studies to ensure the analysis is accurately assessing unintentional exposures and exclude adolescents, this study looked at this age range separately as well as examined cases in different age groups. Other age groups of interest revolved around youth and adolescents. As adolescence varies by individual, sex and national differences, this analysis used age categories of 10-19 years, based on the World Health Organization identification as this time period as the general span of adolescents (World Health Organization, 2017). We also used a category for 20-24 years as this age span is described as late adolescence in the United States (Arnett & Tanner, 2004) and utilized in similar studies in Colorado (Wang et al., 2014).

Unknown age includes teen, unknown adult, unknown 20's and unknown. Adults 30 and over with decade specification but no specific age they were assigned the median of their decade, e.g. 50's was assigned 55. A listing of marijuana-involved exposure calls and aggregate numbers of all PCC exposure calls by age group and by year was provided by the PCC for calls originating from within Massachusetts. We excluded calls from Rhode Island.

We included the following product codes: 310124 Marijuana: Concentrated Extract (Including Oils and Tinctures); 083000 Marijuana: Dried Plant; 310121 Marijuana: Edible Preparation, 310122 Marijuana: Oral Capsule or Pill Preparation, 310126 Marijuana: Other or Unknown Preparation, 200618 Marijuana: Pharmaceutical Preparation, 310125 Marijuana: Topical Preparation, 310123 Marijuana: Undried Plant, 310096 eCigarettes: Marijuana Device Flavor Unknown, 310034 eCigarettes: Marijuana Device With Added Flavors, 310033 eCigarettes: Marijuana Device Without Added Flavors, 310097 eCigarettes: Marijuana Liquid Flavor Unknown, 310036 eCigarettes: Marijuana Liquid With Added Flavors, 310035 eCigarettes: Marijuana Liquid Without Added Flavors. There were five cases exposed to two marijuana codes: one exposure always being dried plant there was 1 synthetic, 2 edibles, 1 concentrate, and 1 other/unknown. These were recoded as 2 marijuana codes. No combination of marijuana preparations exceeded two preparations, for example dried plant and edible. For calls involving multiple substances, we did not have the information on what other substances were involved, for example acetometaphin.

To explore population fluctuations that could influence prevalence, we examined the percent change in the MA population in 2007, 2010, and 2016 within age categories, using census data. If the change was less than 10%, we used 2010 census data to calculate calls per 100,000 people. There was a greater than 10% change in 25-34, 35-44, 60-64, and 65-74 year age groups, but when collapsed into adults 25 and older, there was no significant change. We, therefore, used 2010 census data as the denominator for population prevalence rates.

We graphed trend lines for the percentage of all PCC calls due to marijuana exposure, and graphed the number of exposure calls due to various preparations of marijuana. Medical marijuana became legal in Massachusetts in late 2012, so we examined whether the proportion of all PCC calls due to marijuana was statistically significantly different before this change (2007-2012) versus after (2013-2016). Chi-squared tests or Fisher’s exact tests were used for those analyses. All analyses were stratified by age group.

Results

Episodes of Marijuana-Related Substance Use Treatment

As shown in Table 1, the number of admissions to substance use treatment for marijuana was 2652 in 2014. This represents an increase from 2012 and 2013 levels, but a decrease from the historic levels in the 2004-2010. The prevalence of marijuana-related admissions to treatment was 45 per 100,000 in 2014. This was consistent in the last few years, and a decline from peak levels in 2006-2005 (Figure 1).

Table 1. Number of Substance Abuse Treatment Admissions in Massachusetts by Primary Sub-Substance of Abuse, Age 12+, 2004-2014

Primary Substance	Year										
	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
marijuana	3144	3372	4957	4360	3362	3073	3157	2614	2501	2357	2652
alcohol	20421	20734	37337	36570	32435	32153	31299	28587	27678	26786	27619
opioids	29086	28509	41097	42014	39568	41700	40306	41723	46200	50482	50116
cocaine	3643	4223	7446	6597	4828	4066	3519	3036	2758	2461	2319
meth/amp	119	152	190	163	94	70	126	90	115	160	182
Total	53269	53618	86070	85344	76925	77989	75250	73436	76751	79889	80236

Note: other substances of abuse are not included in this table.

*meth/amp=methamphetamine/amphetamine.

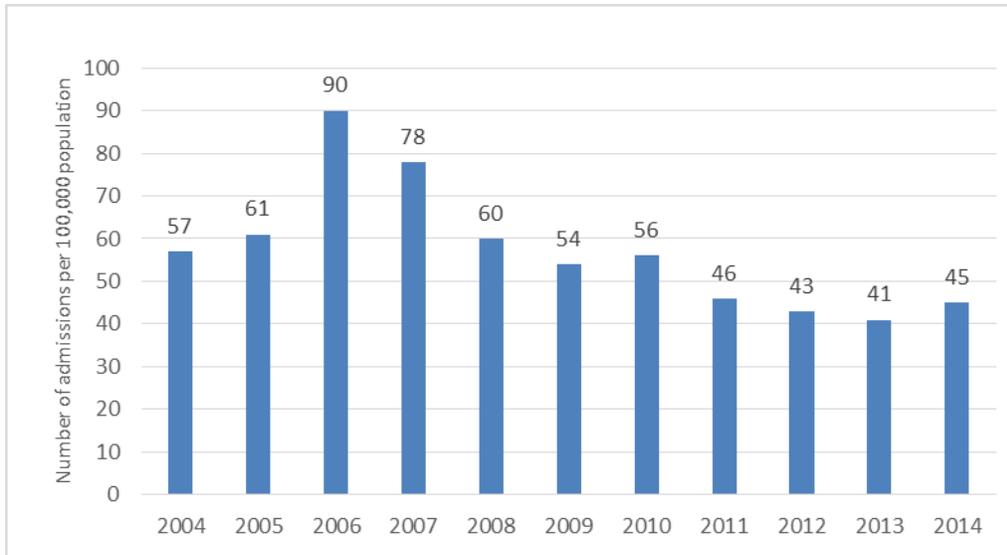


Figure 1. Massachusetts Admissions to Substance Use Treatment with Marijuana as Primary Substance of Abuse, Age 12+, 2004-2014

As shown in Figure 2, the proportion of substance abuse treatment admissions due to marijuana use has remained at less than 5% of all admissions. However, it is important to note that in the midst of the opioid epidemic, which has taxed the capacity of the treatment system, the proportion of admissions due to all other substances would inherently be reduced.

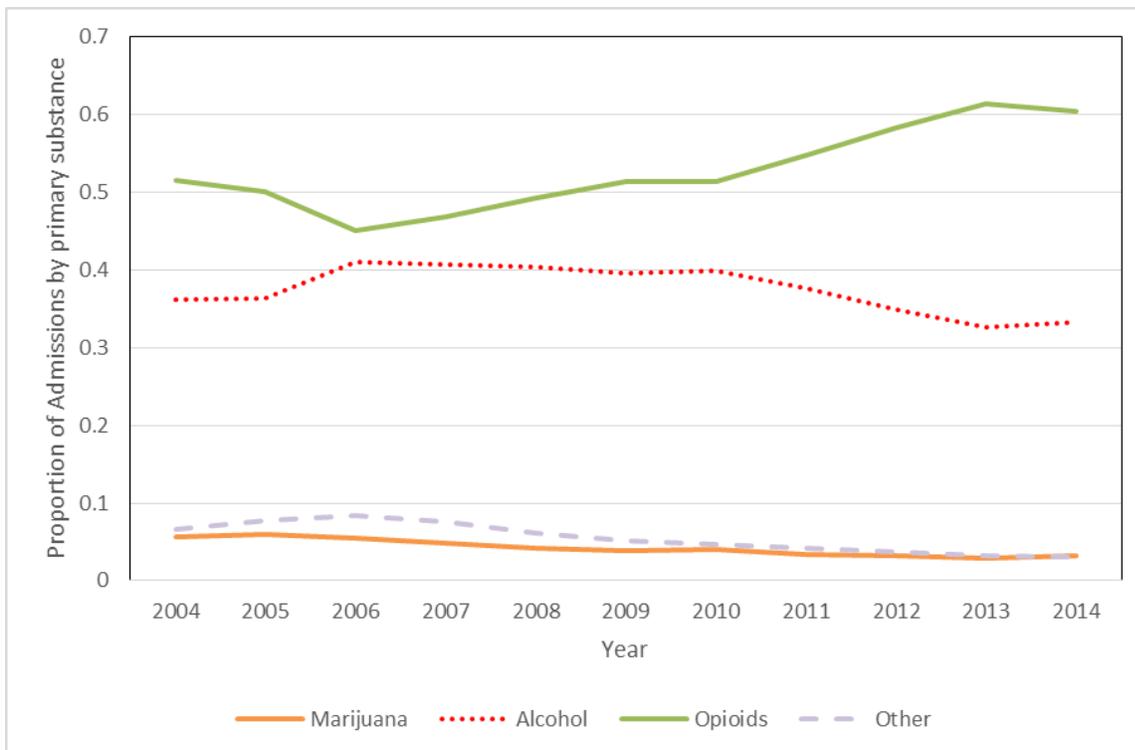


Figure 2. Proportion of Substance Abuse Treatment Admissions by Primary Substance of Abuse, 2004-2014

Substance Use-Related Emergency Care

Among those who used marijuana in the past 30 days, no respondents reported marijuana-related use of emergency room or urgent care services in the prior year. Nearly 70% of Massachusetts adults used alcohol in the past 30 days. Among this group, 1.7% reported use of emergency use of healthcare due to alcohol in the past year. Additionally, 4.1% of the population reported past 30-day use of other substances (e.g. cocaine, opioids, etc.); 4.7% of these individuals sought emergency care related to their substance use, although we note that this estimate is based on fewer than five individuals in the sample and should be interpreted with caution.

Marijuana-Related Exposure Calls to the Poison Control Center

During the 10-year study period (2007-2016) there were 641 calls to the PCC that included marijuana exposure (Table 2) with an upward trend over time (Figure 3). The overall period prevalence from 2007-2016 was 9.4 per 100,000 population. In 2016, there were 78 calls to the PCC with marijuana exposure. Six of these calls pertained to marijuana exposure in youth age 0-9 years, 33 among youth 10-19 years, 12 among young adults age 20-24 years, and 27 among individuals age 25 years and older. These numbers correspond to a prevalence of 0.79 per 100,000 among children age 0-9 years was; 3.8 among 10-19 year olds, 2.5 among 20-24, and 0.6 per 100,000 among those over age 25 years.

For youth under age 18, the proportion of all PCC calls that were due to marijuana, by age group, is shown in Figure 3. The proportion was highest for youth between 10-19 years. Although the magnitude is small, with the highest proportion being under 0.5% (among 10-17 year olds), this is concerning, since the youngest children 0-9 years are being impacted at increasingly levels, presumably through unintentional exposure (Figure 3). We also observed increasing proportions of calls due to marijuana for adults (Figure 4).

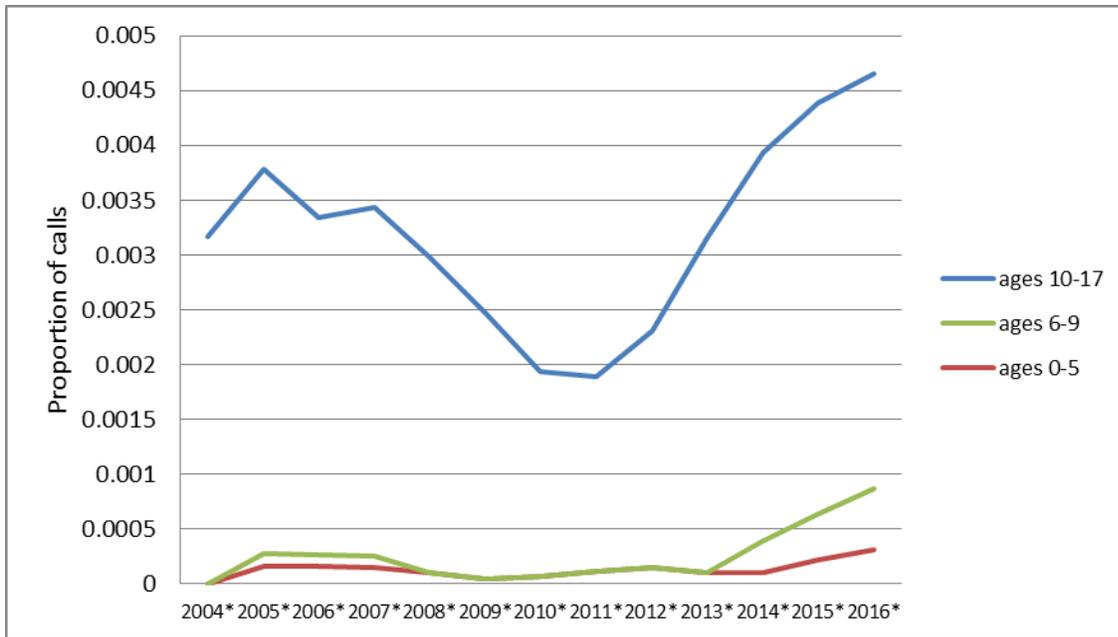


Figure 3. Proportion of MA Poison Control Calls due to Marijuana, Youth Age 0-17, 3-Year Moving Average, and 2004-2016

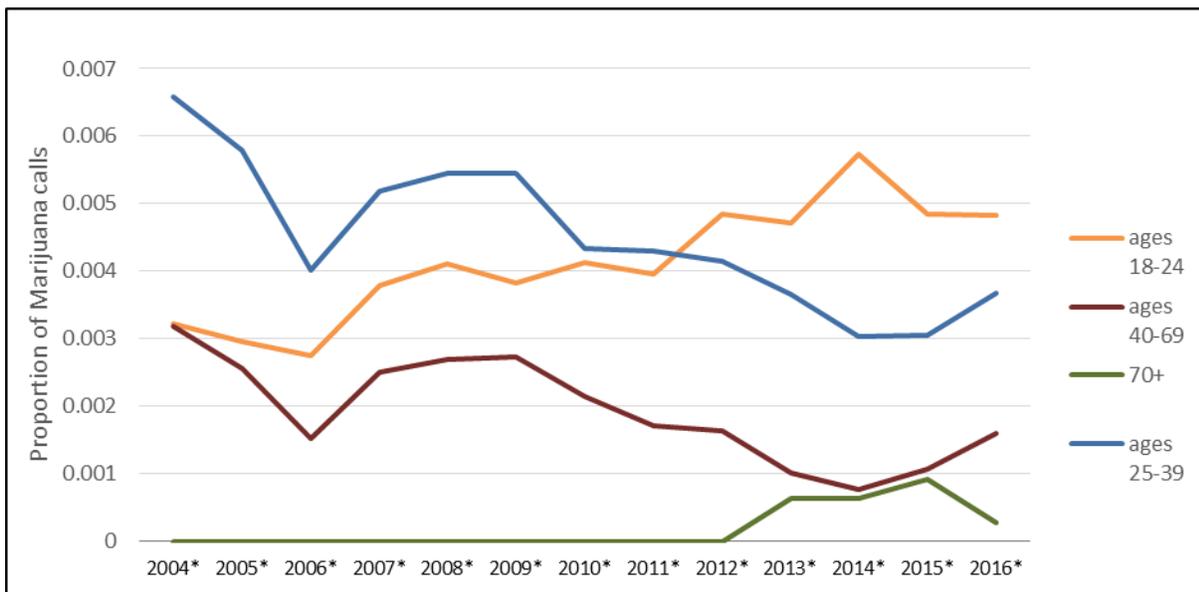


Figure 4. Proportion of MA Poison Control Calls Related to Marijuana Exposure, Adults 18+ Years, 3-Year Moving Average, 2004-2016

Table 2. Demographics and Medical Outcomes of Cannabis-Involved Exposure Calls to the Poison Control Center, Massachusetts, 2007-2016

	Frequency	Percent	
Sex			
Female	253	39.47	
Male	388	60.53	
Total	641	100	
Age			
0-9 years	27	4.21	
10-19 years	257	40.09	
20-24	121	18.88	
25-29	50	7.8	
30's	79	12.32	
40's	53	8.27	
50's	22	3.43	
60's	6	0.94	
70's+	3	0.47	
Unknown	23	3.59	
Total	641	100	
Medical Outcome			No. Calls with One Code[‡]
Death	3	0.47	0 (0%)
major effect	56	8.74	3 (5.4%)
minor effect	143	22.31	31 (22%)
moderate effect	277	43.21	53 (19%)
no effect	36	5.62	9 (25%)
not followed, minimal effects possible	29	4.52	14 (48%)
not followed, non-toxic	4	0.62	4 (100%)
unable to follow, judged potentially toxic	87	13.57	55 (63%)
unrelated effect, exposure probably not responsible for effects	6	0.94	3(50%)
Total	641	100	

One substance was a non-synthetic preparation of Marijuana; Proportion in parentheses represents the proportion of all cannabis-involved calls within each medical outcome that were due to only one cannabis code.

Table 2 shows the medical outcomes reported by PCC professionals. Not surprisingly, there was a higher proportion of calls involving a death or major effect for calls involving multiple substances (as many as 14 involved) compared to calls involving only one cannabis code. The multi-substance calls included substances that were not marijuana. We examined whether there was an increase in the proportion of PCC calls due to marijuana after medical marijuana was legalized in Massachusetts versus before.

Results from chi-squared and Fisher's exact tests indicated that although the percentages are small, there was a higher proportion of PCC calls due to marijuana exposure in 2013-2016 compared to 2007-2012 for children age 0-5 years ($p=0.001$), children 6-9 years ($p=0.017$) and youth age 10-20 ($p=0.001$). See Table 3.

When examining the different marijuana product codes involved in calls to the PCC, we found that over time and across age groups, most calls involved dried marijuana plant. The next most common preparation involved was edible preparations, more frequently seen after 2012 (Figures 5-7).

Table 3. Differences in Proportions of Marijuana-Related Poison Control Center Calls, Pre- versus Post-2012

Ages 0-5						
	2007-2012		2013-2016		total	p-value
	n	%	n	%	n	
Marijuana calls	7	0.008	16	0.035	23	0.001
Non-marijuana calls	84,441	99.992	46,305	99.965	130,846	
Total calls	84,448	100.000	46,321	100.000	130869	
Ages 6-9						
	2007-2012		2013-2016		total	p-value
	n	%	n	%	n	
Marijuana calls	0	0.000	4	0.043	4	0.017
Non-Marijuana calls	16,431	100.000	9,388	99.957	25,919	
Total calls	16431	100.000	9392	100.000	25923	
Ages 10-20						
	2007-2012		2013-2016		total	p-value
	n	%	n	%	n	
Marijuana calls	155	0.291	129	0.439	284	0.001
Non-Marijuana calls	53,286	99.709	29,288	99.561	82,574	
Total calls	53441	100.000	29417	100.000	82858	
Ages 21+						
	2007-2012		2013-2016		total	p-value
	n	%	n	%	n	
Marijuana calls	197	0.332	110	0.278	307	0.145
Non-Marijuana calls	59,107	99.668	39,450	99.722	98,557	
Total calls	59304	100.000	39560	100.000	98864	

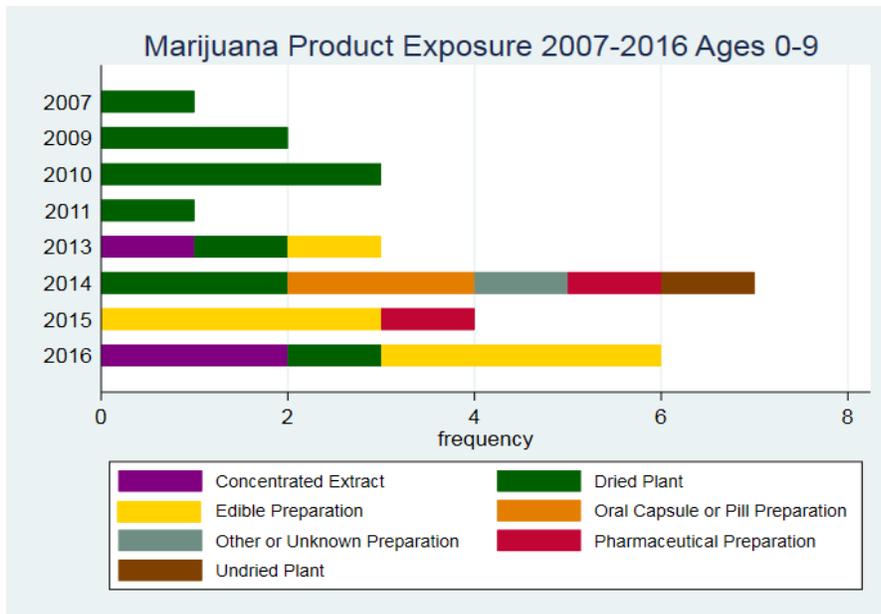


Figure 5. Frequency of Poison Control Center Reported Marijuana Exposures by Product Code, 2007-2016, Age 0-9 Years

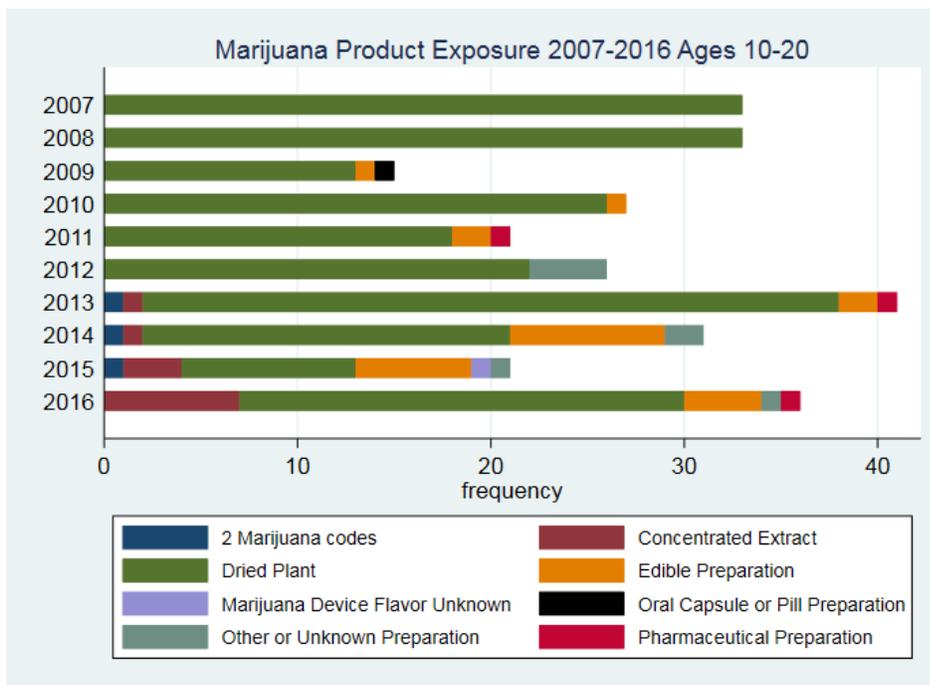


Figure 6. Frequency of Poison Control Center Reported Marijuana Exposures by Product Code, 2007-2016, Age 10-20 Years

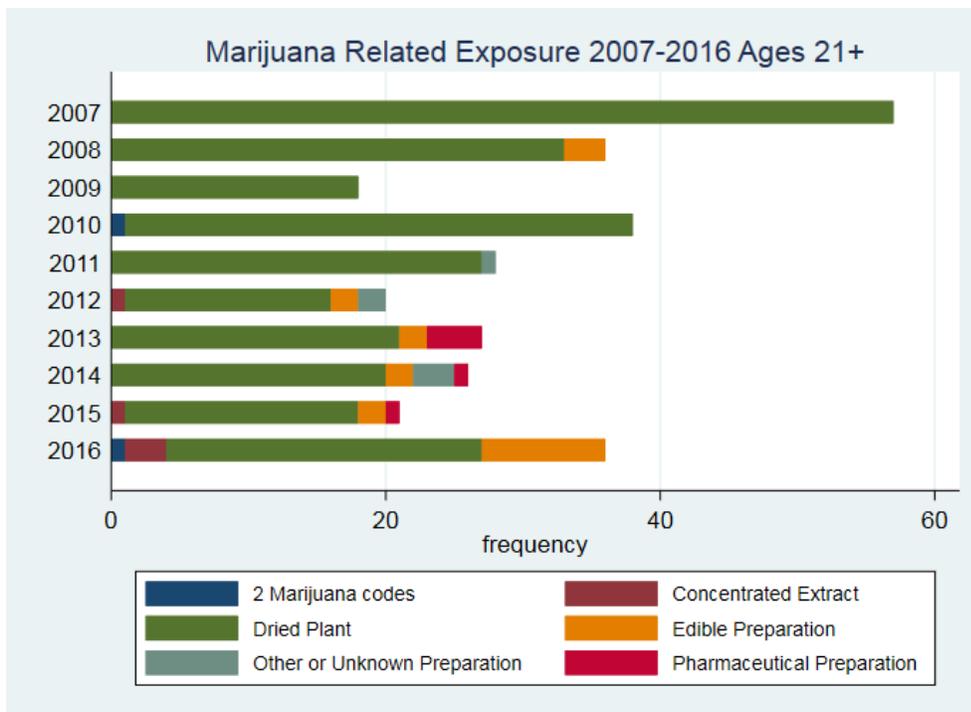


Figure 7. Frequency of Poison Control Center Reported Marijuana Exposures by Product Code, 2007-2016, Age 21 Years and Older

Discussion

In MA from 2005-2016, the period prevalence was 3.5 per 100,000 in children age 0-9 years. A study of Colorado between 2005 and 2011 found cases of children under the age of 9 who had Poison control calls for marijuana related exposures was 6.6 per 100,000; this was compared to generally less than 2 calls per 100,000 in states without similar marijuana legislation (Wang et al., 2014). That study raised discussions about whether the finding of increased prevalence in a state with medical marijuana at the time was due to increased exposure or less stigma among parents or caregivers calling to report such an exposure (Hoffman, 2016). Our data indicated that there was a statistically significant increase in the proportion of calls to the PCC that were related to marijuana after medical marijuana was legalized in Massachusetts.

Children age 0-9 years accounted for less than 5% of the calls to the PCC due to marijuana exposure during the study period, whereas youth aged 10-19 years accounted for 40% of marijuana-related calls.

References

- Alcohol and Drug Abuse Institute. (2013). What is Cannabis? Retrieved from <http://learnaboutmarijuana.org/factsheets/whatiscannabis.htm>
- Alere DDS®2 Mobile Test System: Rapid Screening for Drugs of Abuse in Oral Fluid. (2018). Retrieved from <https://www.alere.com/en/home/product-details/dds2-mobile-test-system.html#>
- Allen, K. R. (2011). Screening for drugs of abuse: which matrix, oral fluid or urine? *Annals of Clinical Biochemistry*, 48(6), 531-541.
- Arnett, J. J., & Tanner, J. L. (Eds.). (2004). *Emerging Adulthood: The Winding Road from the Late Teens through the Twenties*. New York, NY: Oxford University Press.
- Arria, A. M., Caldeira, K. M., Vincent, K. B., Garnier-Dykstra, L. M., & O'Grady, K. E. (2011). Substance-related traffic-risk behaviors among college students. *Drug Alcohol Depend*, 118(2-3), 306-312. doi:10.1016/j.drugalcdep.2011.04.012
- Asbridge, M., Hayden, J. A., & Cartwright, J. L. (2012). Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *BMJ*, 344, e536.
- Banta-Green, C., Rowhani-Rahbar, A., Ebel, B. E., Andris, L. M., & Qiu, Q. (2016). Cannabis Use among Drivers Suspected of Driving Under the Influence or Involved in Collisions: Analyses of Washington State Patrol Data.
- Berning, A., & Smither, D. (2014). *Understanding the Limitations of Drug Test Information, Reporting, and Testing Practices in Fatal Crashes*. Washington, D.C.: U. S. D. o. Transportation. Retrieved from
- Blencowe, T., Pehrsson, A., & Lillsunde, P. (2010). *Analytical evaluation of oral fluid screening devices and preceding selection procedures*. A. a. M. Driving Under the Influence of Drugs. Retrieved from https://www.bast.de/Druid/EN/deliverables-list/downloads/Deliverable_3_2_2.pdf?_blob=publicationFile&v=1.
- Bondallaz, P., Favrat, B., Chtioui, H., Fornari, E., Maeder, P., & Giroud, C. (2016). Cannabis and its effects on driving skills. *Forensic Sci Int*, 268, 92-102. doi:<https://doi.org/10.1016/j.forsciint.2016.09.007>
- Bosker, W. M., & Huestis, M. A. (2009). Oral fluid testing for drugs of abuse. *Clin Chem*, 55(11), 1910-1931.
- Chihuri, S., Li, G., & Chen, Q. (2017). Interaction of marijuana and alcohol on fatal motor vehicle crash risk: a case-control study. *Inj Epidemiol*, 4(1), 8. doi:10.1186/s40621-017-0105-z
- Compton, R. (2017). *Marijuana-Impaired Driving A Report to Congress*. Washington, DC. Retrieved from
- Davis, K. C., Allen, J., Duke, J., Nonnemaker, J., Bradfield, B., Farrelly, M. C., . . . Novak, S. (2016). Correlates of Marijuana Drugged Driving and Openness to Driving While High: Evidence from Colorado and Washington. *PLoS One*, 11(1), e0146853. doi:10.1371/journal.pone.0146853
- Department of Health and Environment, C. Adult marijuana use trends. *Monitoring trends in adult marijuana use*.
- Department of Health and Human Services. (2015). *Mandatory Guidelines for Federal Workplace Drug Testing Programs*. Retrieved from
- Dräger DrugTest® 5000: Analysis system for detecting drugs. (2018). Retrieved from https://www.draeger.com/Library/Content/drugtest_5000_pi_9041006_en.pdf
- Drummer, O. H. (2010). Forensic toxicology. *Exs*, 100, 579-603.
- Edwards, L. D., Smith, K. L., & Savage, T. (2017). Drugged Driving in Wisconsin: Oral Fluid Versus Blood. *J Anal Toxicol*, 41(6), 523-529. doi:10.1093/jat/bkx051

- Gentili, S., Solimini, R., Tittarelli, R., Mannocchi, G., & Busardo, F. P. (2016). A Study on the Reliability of an On-Site Oral Fluid Drug Test in a Recreational Context. *J Anal Methods Chem*, 2016, 1234581. doi:10.1155/2016/1234581
- Gentili, S., Solimini, R., Tittarelli, R., Mannocchi, G., & Busardò, F. P. (2016). A Study on the Reliability of an On-Site Oral Fluid Drug Test in a Recreational Context. *J Anal Methods Chem*, 2016, 1234581. doi:10.1155/2016/1234581
- Grotenhermen, F. (2003). Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*, 42(4), 327-360. doi:10.2165/00003088-200342040-00003
- Gunasekaran, N., Long, L. E., Dawson, B. L., Hansen, G. H., Richardson, D. P., Li, K. M., . . . McGregor, I. S. (2009). Reintoxication: the release of fat-stored $\Delta(9)$ -tetrahydrocannabinol (THC) into blood is enhanced by food deprivation or ACTH exposure. *British Journal of Pharmacology*, 158(5), 1330-1337. doi:10.1111/j.1476-5381.2009.00399.x
- Hartman, R. L., Anizan, S., Jang, M., Brown, T. L., Yun, K. M., Gorelick, D. A., . . . Huestis, M. A. (2015). Cannabinoid disposition in oral fluid after controlled vaporizer administration with and without alcohol. *Forensic Toxicology*, 33(2), 260-278. doi:10.1007/s11419-015-0269-6
- Hartman, R. L., Brown, T. L., Milavetz, G., Spurgin, A., Gorelick, D. A., Gaffney, G., & Huestis, M. A. (2016). Controlled vaporized cannabis, with and without alcohol: subjective effects and oral fluid-blood cannabinoid relationships. *Drug Test Anal*, 8(7), 690-701. doi:10.1002/dta.1839
- Hoffman, J. (2016). Study finds sharp increase in marijuana exposure among Colorado children. *The New York Times*. Retrieved from <https://www.nytimes.com/2016/07/26/health/marijuana-edibles-are-getting-into-colorado-childrens-hands-study-says.html>
- Hollister, L. E., Gillespie, H. K., Ohlsson, A., Lindgren, J. E., Wahlen, A., & Agurell, S. (1981). Do plasma concentrations of delta 9-tetrahydrocannabinol reflect the degree of intoxication? *J Clin Pharmacol*, 21(8-9 Suppl), 171s-177s.
- Huestis, M. A. (2002). Cannabis (Marijuana) - Effects on Human Performance and Behavior. *Forensic Sci Rev*, 14(1-2), 15-60.
- Huestis, M. A. (2007). Human Cannabinoid Pharmacokinetics. *Chemistry & biodiversity*, 4(8), 1770-1804. doi:10.1002/cbdv.200790152
- Huestis, M. A., Milman, G., Mendu, D., Lee, D., Barnes, A. J., Schwoppe, D., . . . Desrosier, N. A. (2013). *Evaluation the on-site Draeger DrugTest 5000 in occasional and chronic frequent smokers following controlled cannabis smoking*. Retrieved from http://www.icadtsinternational.com/files/documents/2013_058.pdf.
- Huestis, M. A., Milman, G., Mendu, D., Lee, D., Barnes, A. J., Schwoppe, D. M., . . . Desrosiers, N. A. (2013). *Evaluation of the on-site Draeger DrugTest 5000 in occasional and chronic frequent smokers following controlled cannabis smoking*. Paper presented at the International Conference on Alcohol, Drugs and Traffic Safety (T2013), 20th, 2013, Brisbane, Queensland, Australia.
- Huestis, M. A., & Smith, M. L. (2018). Cannabinoid Markers in Biological Fluids and Tissues: Revealing Intake. *Trends Mol Med*, 24(2), 156-172. doi:10.1016/j.molmed.2017.12.006
- Kim, S. Y., Kim, H., Park, Y., Lim, J., Kim, J., Koo, S. H., & Kwon, G. C. (2017). Evaluation of an Automated Reader and Color Interpretation-Based Immunoassays for Multiplexed Drug-of-Abuse Testing in Urine. *J Anal Toxicol*, 41(5), 412-420. doi:10.1093/jat/bkx014
- Lee, D., Milman, G., Barnes, A. J., Goodwin, R. S., Hirvonen, J., & Huestis, M. A. (2011). Oral fluid cannabinoids in chronic, daily cannabis smokers during sustained, monitored abstinence. *Clin Chem*, 57(8), 1127-1136.

- Li, G., Chihuri, S., & Brady, J. E. (2017). Role of alcohol and marijuana use in the initiation of fatal two-vehicle crashes. *Annals of Epidemiology*, 27(5), 342-347.e341. doi:<https://doi.org/10.1016/j.annepidem.2017.05.003>
- Li, K., Simons-Morton, B., Gee, B., & Hingson, R. (2016). Marijuana-, alcohol-, and drug-impaired driving among emerging adults: Changes from high school to one-year post-high school. *J Safety Res*, 58, 15-20. doi:10.1016/j.jsr.2016.05.003
- Macdonald, S., Anglin-Bodrug, K., Mann, R. E., Erickson, P., Hathaway, A., Chipman, M., & Rylett, M. (2003). Injury risk associated with cannabis and cocaine use. *Drug Alcohol Depend*, 72(2), 99-115.
- Milburn, M. (2017). DRUID. Retrieved from <https://www.druidapp.com>
- Moore, C., Coulter, C., Uges, D., Tuyay, J., Van der Linde, S., Van Leeuwen, A., . . . Orbita Jr, J. (2011). Cannabinoids in oral fluid following passive exposure to marijuana smoke. *Forensic Sci Int*, 212(1-3), 227-230.
- National Highway Traffic Safety Administration. (2016a). *2016 FARS/CRSS Coding and Validation Manual*. Washington, D.C: National Highway Traffic Safety Administration. Retrieved from <https://crashstats.nhtsa.dot.gov/Api/Public/Publication/812449>.
- National Highway Traffic Safety Administration. (2016b). *Fatality Analysis Reporting System (FARS) Analytical User's Manual 1974-2015*. Washington, D.C.: U. S. D. o. Transportation. Retrieved from <http://www.nber.org/fars/ftp.nhtsa.dot.gov/fars/FARS-DOC/Analytical%20User%20Guide/USERGUIDE-2015.pdf>.
- Newmeyer, M. N., Swortwood, M. J., Andersson, M., Abulseoud, O. A., Scheidweiler, K. B., & Huestis, M. A. (2017a). Cannabis Edibles: Blood and Oral Fluid Cannabinoid Pharmacokinetics and Evaluation of Oral Fluid Screening Devices for Predicting Delta9-Tetrahydrocannabinol in Blood and Oral Fluid following Cannabis Brownie Administration. *Clin Chem*, 63(3), 647-662. doi:10.1373/clinchem.2016.265371
- Newmeyer, M. N., Swortwood, M. J., Andersson, M., Abulseoud, O. A., Scheidweiler, K. B., & Huestis, M. A. (2017b). Cannabis Edibles: Blood and Oral Fluid Cannabinoid Pharmacokinetics and Evaluation of Oral Fluid Screening Devices for Predicting Delta(9)-Tetrahydrocannabinol in Blood and Oral Fluid following Cannabis Brownie Administration. *Clin Chem*, 63(3), 647-662. doi:10.1373/clinchem.2016.265371
- Newmeyer, M. N., Swortwood, M. J., Barnes, A. J., Abulseoud, O. A., Scheidweiler, K. B., & Huestis, M. A. (2016). Free and Glucuronide Whole Blood Cannabinoids' Pharmacokinetics after Controlled Smoked, Vaporized, and Oral Cannabis Administration in Frequent and Occasional Cannabis Users: Identification of Recent Cannabis Intake. *Clin Chem*, 62(12), 1579-1592. doi:10.1373/clinchem.2016.263475
- Quantisal™ Oral Fluid Collection Device. (2018). Retrieved from <https://www.alere.com/en/home/product-details/QuantisalOralFluidCollectionDevice-au.html>
- Rocky Mountain High Intensity Drug Trafficking Area. (2015). *The Legalization of Marijuana in Colorado: The Impact*.
- Rogeberg, O., & Elvik, R. (2016). The effects of cannabis intoxication on motor vehicle collision revisited and revised. *Addiction*, 111(8), 1348-1359. doi:10.1111/add.13347
- Salomonsen-Sautel, S., Min, S. J., Sakai, J. T., Thurstone, C., & Hopfer, C. (2014). Trends in fatal motor vehicle crashes before and after marijuana commercialization in Colorado. *Drug Alcohol Depend*, 140, 137-144. doi:10.1016/j.drugalcdep.2014.04.008
- Scherer, J. N., Fiorentin, T. R., Borille, B. T., Pasa, G., Sousa, T. R. V., von Diemen, L., . . . Pechansky, F. (2017). Reliability of point-of-collection testing devices for drugs of abuse in oral fluid: A systematic review and meta-analysis. *Journal of Pharmaceutical and Biomedical Analysis*, 143, 77-85. doi:10.1016/j.jpba.2017.05.021
- Subramanian, R. (2002). *Transitioning to multiple imputation - A New method to estimate missing blood alcohol concentration (BAC) in FARS*. Springfield, VA: National Center for

- Statistics and Analysis. Retrieved from <https://crashstats.nhtsa.dot.gov/Api/Public/ViewPublication/809403>.
- Swortwood, M. J., Newmeyer, M. N., Abulseoud, O. A., Andersson, M., Barnes, A. J., Scheidweiler, K. B., & Huestis, M. A. (2017). On-site oral fluid Delta(9)-tetrahydrocannabinol (THC) screening after controlled smoked, vaporized, and oral cannabis administration. *Forensic Toxicology*, *35*(1), 133-145. doi:10.1007/s11419-016-0348-3
- Tefft, B. C., Arnold, L. S., & Grabowski, J. G. (2016). Prevalence of Marijuana Involvement in Fatal Crashes: Washington, 2010–2014.
- Verstraete, A., Knoche, A., Jantos, R., Skopp, G., Gjerde, H., Vindenes, V., . . . Lillsunde, P. (2011). Per se limits: methods of defining cut-off values for zero tolerance.
- Wall, M. E., Sadler, B. M., Brine, D., Taylor, H., & Perez-Reyes, M. (1983). Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. *Clin Pharmacol Ther*, *34*(3), 352-363.
- Walsh, J. M. (2008). New technology and new initiatives in US workplace testing. *Forensic Sci Int*, *174*(2-3), 120-124. doi:10.1016/j.forsciint.2007.03.011
- Walsh, J. M., Verstraete, A. G., Huestis, M. A., & Mørland, J. (2008). Guidelines for research on drugged driving. *Addiction*, *103*(8), 1258-1268.
- Wang, G. S., Roosevelt, G., Le Lait, M. C., Martinez, E. M., Bucher-Bartelson, B., Bronstein, A. C., & Heard, K. (2014). Association of unintentional pediatric exposures with decriminalization of marijuana in the United States. *Ann Emerg Med*, *63*(6), 684-689. doi:10.1016/j.annemergmed.2014.01.017
- Westin, A. A., Mjønes, G., Burchardt, O., Fuskevåg, O. M., & Slørdal, L. (2014). Can Physical Exercise or Food Deprivation Cause Release of Fat-Stored Cannabinoids? *Basic & Clinical Pharmacology & Toxicology*, *115*(5), 467-471. doi:10.1111/bcpt.12235
- Whitehill, J. M., Rivara, F. P., & Moreno, M. A. (2014). Marijuana-using drivers, alcohol-using drivers, and their passengers: prevalence and risk factors among underage college students. *JAMA Pediatr*, *168*(7), 618-624. doi:10.1001/jamapediatrics.2013.5300
- Wong, A., Keats, K., Rooney, K., Hicks, C., Allsop, D. J., Arnold, J. C., & McGregor, I. S. (2014). Fasting and exercise increase plasma cannabinoid levels in THC pre-treated rats: an examination of behavioural consequences. *Psychopharmacology (Berl)*, *231*(20), 3987-3996. doi:10.1007/s00213-014-3532-3
- Wong, A., Montebello, M. E., Norberg, M. M., Rooney, K., Lintzeris, N., Bruno, R., . . . McGregor, I. S. (2013). Exercise increases plasma THC concentrations in regular cannabis users. *Drug Alcohol Depend*, *133*(2), 763-767. doi:10.1016/j.drugalcdep.2013.07.031
- Wood, E., Brooks-Russell, A., & Drum, P. (2016). Delays in DUI blood testing: Impact on cannabis DUI assessments. *Traffic Inj Prev*, *17*(2), 105-108. doi:10.1080/15389588.2015.1052421
- World Health Organization. (2017). Adolescent Health. Retrieved from http://www.who.int/topics/adolescent_health/en/
- Zou, G. (2004). A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*, *159*(7), 702-706.

Task 3: Economic and Fiscal Impacts

Chapter 1: From Medical to Retail Marijuana: Estimating Fiscal Effects of Legalization In Massachusetts

Abstract

Background

In 2016, Massachusetts voters approved a ballot measure to legalize broad adult use of marijuana. As part of the 2017-2018 Massachusetts Marijuana Baseline Health Study, we estimated fiscal impacts of legalization for state and local governments. We developed a model to estimate changes expected in four key domains within the first two years of retail sales: tax revenue from marijuana purchases (based on a 20% combined sales, excise, and local tax rate); regulatory oversight; law enforcement activities; and public health effects.

Methods

Estimates of revenue or savings and costs or losses were derived from the literature (restricted to impacts attributable to legalization); expert interviews; and secondary sources (on marijuana pricing, marijuana use prevalence, regulatory costs and revenue, public health and safety outcomes, and Massachusetts population size and demographics). For each measure, we defined a range of values, then used Monte Carlo simulation to randomly choose a value to calculate post-legalization estimate. We calculated post-legalization impacts by combining information on pre-legalization estimates with estimates of change due to legalization. We summed estimates across all measures and domains to obtain an overall impact estimate.

Results

In our main model, which included measures that were major drivers of budgetary impacts (sales and business tax revenue, regulatory costs and revenue, and savings due to reduced marijuana-related law enforcement), we projected a gain of \$215.8 million to the state budget. In a supplemental model that added in public health impacts thought to be less definitive or immediate, we projected an additional gain of \$65.3 million, yielding a total impact of \$281.1 million. Local tax revenue estimates (derived using local data on marijuana use prevalence and pricing, when available) ranged from a median of \$63,000 for suburban cities and towns to \$583,000 for urban cities.

Discussion

The primary driver of fiscal gains (accounting for 53% of the total impact) was sales and excise tax revenue collected on retail marijuana purchases. Other major contributors included new business tax revenue from marijuana dispensaries and increased individual income tax revenue due to worker productivity gains among older adults who are able to control debilitating medical conditions with marijuana.

Background

In November 2016, Massachusetts voters approved a ballot measure to legalize adult use of marijuana, joining a growing list of states approving and implementing similar measures in the past five years. The adult use of marijuana program will build on the medical marijuana program that has been operating in Massachusetts since 2013, serving nearly 50,000 active patients as of January 2018.¹ The program will also build on the experiences from other states that have legalized marijuana in recent years. However, given that retail sales of marijuana have only been legal in the United States for about four years, there is a sparse body of literature on the causal impacts of marijuana on a host of fiscal, health, public safety, and criminal justice outcomes. To better understand marijuana use in the state and to project fiscal impacts associated with retail sales, the state legislated that the Massachusetts Department of Public Health (MDPH) conduct the Marijuana Baseline Health Study (MBHS). The study examines the use, methods of consumption, and perceptions of marijuana; impaired driving and hospitalization related to marijuana use; and economic and fiscal impacts for state and local governments.² In this report, we address the third aim to estimate the fiscal impacts of moving from a medical marijuana program to broad adult use. We focus on four key domains: (1) tax revenue from marijuana sales, (2) regulatory oversight, (3) law enforcement activities, and (4) public health effects.

Retail sales of marijuana are planned to begin in July 2018, after legislation was passed in December 2016 to delay implementation of the program by six months.³ Whereas the original ballot measure included a 3.75% excise tax, 6.25% state sales tax, and an optional local tax up to 2%, for a maximum tax rate of 12%, the state legislature later passed a bill to increase the excise tax to 10.75% and the maximum local tax to 3%, yielding a total maximum tax rate of 20%.⁴ A share of the revenues collected by the state will be devoted to (1) public and behavioral health, (2) public safety, (3) municipal police training, (4) the Prevention and Wellness Trust Fund, and (5) a host of services for “economically-disadvantaged persons in communities disproportionately impacted by high rates of arrest and incarceration for marijuana offenses.”⁵

The existing medical marijuana program in Massachusetts registers nonprofit organizations to cultivate and dispense marijuana as well as patients and physicians.⁶ As of January 2018, the program had 227 registered certifying health care providers and nearly 50,000 active patients. The program has consistently added roughly 2,000 patients per month over its history. There are 22 registered marijuana dispensaries with final certification and approval to sell, 6 with final certification but not yet approved to

¹ <https://www.mass.gov/lists/medical-use-of-marijuana-program-monthly-dashboards>.

² Mass. Session Laws ch. 351, § 18 (2016).

³ Mass. Gen. Laws ch. 94G, § 14.

⁴ Mass. Session Laws ch. 55, § 12 (2017).

⁵ Mass. Gen. Laws ch. 94G, § 14.

⁶ <https://www.mass.gov/medical-use-of-marijuana-program>.

sell, and 99 with provisional certificates and in the inspection phase. In contrast to the adult use program, the medical program requires those selling medical marijuana to follow a seed-to-sale model—that is, the same entity is responsible for the product from cultivation to sale in licensed dispensaries. In addition, the marijuana is not subject to any taxes, and only nonprofit organizations can participate.

To implement and administer the adult use program and create a safely regulated industry, the state formed the Cannabis Control Commission (CCC) in 2017. The CCC will also take over regulatory activities for the medical marijuana program, currently administered by the MDPH Bureau of Health Care Safety and Quality.⁷ Massachusetts also created the Cannabis Advisory Board, a 25-member group charged with studying and making recommendations to the CCC on the regulation and taxation of marijuana in Massachusetts.

The adult use program in Massachusetts and the study presented here have the benefit of learning from experiences in several other states that have implemented similar programs in the past four years. Colorado and Washington approved ballot measures in 2013 to legalize marijuana for adult use and began retail sales in 2014. In 2014, Alaska, Oregon, and Washington, D.C. voted to legalize adult use, with retail sales beginning in 2015 in Oregon and in 2016 in Alaska; retail sales are not yet permitted in Washington, D.C. In 2016, California, Maine, Nevada, and Massachusetts approved ballot measures, with retail sales beginning in 2017 in Nevada and 2018 in California and Massachusetts; retail sales are not yet permitted in Maine. Finally, the state legislature in Vermont legalized adult use in 2018. Although the experiences with adult use of marijuana in these states have been brief, the states consistently saw substantial increases in revenue collected from retail sales after the first year. Revenue collected in the first year ranged from \$1.7 million in Alaska to \$67.6 million in Colorado.⁸ There were substantial increases in the second and third years of the programs; for example, the revenue collected by the Washington Liquor Cannabis Board (LCB) increased from \$64.9 million in the first year of the program to \$314.8 million in the third year (Washington State LCB, n.d.). In addition, the revenue collected was substantially above the amount projected by the states prior to implementation. Finally, there is some limited evidence suggesting that marijuana legalization could have positive impacts on public health and safety outcomes and criminal justice costs and outcomes (such as reduced incarcerations); however, the evidence is primarily for impacts from medical marijuana legalization, little evidence establishes causal links between legalization and the outcomes, and the timeline for observing impacts for legalization is brief (four years at most for the earliest implementers).

There are a handful of differences between the planned program in Massachusetts and other states that will likely affect the implementation and impact of legalization. First,

⁷ <https://mass-cannabis-control.com/about-us-2/>.

⁸ Alaska: <http://tax.alaska.gov/programs/programs/reports/monthly/Marijuana.aspx?ReportDate=8/1/2017>; Colorado: <https://www.colorado.gov/pacific/revenue/colorado-marijuana-tax-data>; for a summary of revenue collected, see <http://www.drugpolicy.org/legalization-status-report>.

other states have implemented substantially higher tax rates than the planned 17% tax rate in Massachusetts (excluding the local tax rate), which influences the price of marijuana in the licit market and thus how much demand is met by retail sales versus the black market. In high-tax Washington (44% point-of-sale tax, excluding the local tax rate), despite the fact that the licit price of marijuana has dropped over time and is only slightly above black market prices, licensed sales account for only about 30% of demand; the rest is met by the state's loosely regulated medical marijuana market and other black market sources.⁹ By contrast, in Colorado, where marijuana taxes were lower (27.9% combined tax rate through July 2017, excluding the local tax rate), an estimated 70% of demand is met by the licit market, with much of the remaining demand met by legal home-grown product. Differences in the structure of the medical marijuana programs will also influence the impact of legalization. The cultivation and sale of medical marijuana is strictly regulated and less accessible to Massachusetts residents compared to other states. Out of 27 states with medical marijuana programs, Massachusetts ranks 15th highest in terms of the number of medical marijuana patients per 1,000 state residents (Marijuana Policy Project, 2018); programs in California, Colorado, and Oregon include a much greater proportion of residents.¹⁰ On the other hand, other states apply taxes to medical marijuana sales to varying degrees; the fact that the Massachusetts medical marijuana program is untaxed could make it more attractive to marijuana consumers once retail sales begin.

In this study, we combine evidence from implementation in other states with the details and nuances of Massachusetts programs and residents to estimate fiscal impacts of legalizing adult use of marijuana on state and local budgets. We estimate impacts separately for key domains of interest: (1) sales and business tax revenue from retail marijuana sales, (2) law enforcement costs, (3) the costs of regulatory oversight, and (4) estimated impacts on state public health expenditures and individual income tax revenue as a result of changes in worker productivity (both of which were included in a supplemental model). Our estimates reflect impacts expected only within the first two years after retail sales are allowed but also include start-up costs and revenue. Given the uncertainty of many of the inputs used to estimate impacts in some of these domains (for example, the projected price of marijuana in the retail market or the percentage of current users that will purchase their marijuana in the licit market), we conducted a number of sensitivity analyses to test the robustness of the results to our inputs. The results generated in the study will help the state and municipalities plan for the impacts of legalization while also providing a point of comparison for early impacts once the program is implemented. Furthermore, the study will provide valuable information to other states considering legalization on the complex public health, public safety, and economic impacts of legalizing marijuana.

⁹ <http://www.denverpost.com/2016/01/06/washington-state-marijuana-retailers-cope-with-falling-pot-prices/> and <https://www.economist.com/news/briefing/21692873-growing-number-countries-are-deciding-ditch-prohibition-what-comes>.

¹⁰ <https://medicalmarijuana.procon.org/view.resource.php?resourceID=005889>.

Methods

Data Sources

We developed a model to estimate changes expected in four key domains within the first two years of retail sales. Each domain (for example, marijuana sales tax revenue) included individual measures (for example, marijuana use prevalence and the price of marijuana) that we estimated using three main sources of information: existing literature, interviews with academic and government experts, and secondary data sources. For each measure that fed into the model, we defined a range of plausible values as follows:

- If multiple (high quality, rigorous) studies or sources estimated the same metric, we defined the range based on the point estimates from these sources.
- If only a single study was used to estimate a metric, we defined the range based on the confidence interval around the point estimate from that paper.
- If there was no credible study or source for a given metric, we estimated a range using information from other states with legalized adult use or from expert stakeholder input.

Literature Review

To inform estimates of the impact of legalization in Massachusetts, we first reviewed the literature on the impacts of marijuana laws or policies on consumption of marijuana, alcohol, and tobacco; public health; public safety; and worker productivity. We also used the literature to identify major sources of direct costs and revenue stemming from marijuana legalization, plus demographic subgroups that are affected differentially by legalization. As a starting point, we first searched peer-reviewed publications based on key search terms (such as “marijuana” and “legalization”) applied to the MEDLINE®, Scopus, and EconLit databases. To avoid excluding potentially relevant search results, we used a broad set of search terms related to marijuana legalization rather than searching by specific terms related to consumption, public health, public safety, and labor productivity. We then searched the gray literature to identify working papers from the National Bureau of Economic Research, research briefs, and other reports published from policy institutes and state governments. After excluding papers based on a review of titles, we reviewed the abstracts to ascertain relevance. We identified 57 candidate papers, to which we uniformly applied a set of causal evidence criteria, as described below, to determine inclusion.

Because the literature has focused mostly on medical marijuana legalization, and there is limited literature on adult use legalization, many of the model impacts derived from the literature are based on the experiences of medical marijuana programs. To account for the possibility that these impacts will not accurately reflect the experience of legalization in Massachusetts, we incorporate ranges for estimates derived from this literature, along with a sensitivity analysis that removes all impacts taken from the medical marijuana literature.

Causal Criteria

To ensure that our model estimates are based only on papers that demonstrate strong causal evidence that links outcomes directly to marijuana policies, we developed a set of guidelines to determine inclusion of impacts in our model estimates.¹¹ We rated each paper based on the strength of evidence as high, moderate, or low causal evidence for marijuana-attributable impacts. A high rating indicates that the analysis meets high methodological standards (for example, with a control group included in the analysis) and the impacts estimated are credible; it does not mean that the study found positive impacts. A moderate causal evidence rating means that we are somewhat confident that the estimated impacts are attributable to the intervention studied, but other factors that were not included in the analysis could have contributed to the impacts observed. Research not meeting the criteria for a high or moderate causal evidence rating received a low causal evidence rating, indicating that we could not be certain that the impacts observed were attributable to the marijuana law or policy being studied. To derive estimates for our model measures, we relied only on studies with a high causal rating. Of the 57 candidate papers reviewed, 16 met the criteria for high causal evidence. As our research progressed, we identified an additional 3 papers published in 2017 that had high causal evidence, resulting in a total of 19 (out of 60) that met our criteria for high quality evidence of impacts attributed to marijuana.

An implication of applying these strict causal guidelines to our inclusion criteria is that we ultimately excluded some studies and state government reports that used longitudinal data to examine how public health and safety outcomes (such as emergency room visits, suicides, and non-fatal crashes) changed after adult use of marijuana was legalized because these analyses lacked valid comparison groups. Our exclusion of these studies does not imply that the results are not valid or useful for certain purposes, but rather that we cannot be confident that the pre-post changes are attributable to legalization.

Stakeholder Interviews

For certain domains of interest, there was insufficient rigorous evidence from the literature on causal impacts of legalization to inform our model estimates. Instead, we gathered information from interviews with expert stakeholders in Massachusetts and other states with legalized marijuana retail sales as well as from researchers studying marijuana legalization. We also used these interviews to gain insight into contextual differences between Massachusetts and other states with legalized adult use that may affect our modeling approach or interpretation of estimates. We interviewed experts in the following knowledge areas: (1) regulatory costs to state and local governments, (2) regulation of the current Massachusetts medical marijuana program, (3) the degree of shift from illicit to legal consumption, (4) current law enforcement practices in Massachusetts, and (5) public health experiences and budget expenditures in Colorado. For each interview, we developed separate protocols with tailored questions that we

¹¹ These guidelines follow the Clearinghouse for Labor Evaluation and Research (CLEAR). CLEAR was established by the Department of Labor to promote informed decision making and policy development by providing a central and trusted source of research evidence.

asked in person, by phone, or through email correspondences. Our notes from these interviews informed the model estimates for measures and domains of interest, as detailed in Table 1.

Table 1. Model Measures Informed by Stakeholder Interviews

Domain	Interviewee's institution	Model measure informed by interview
Tax revenue	Harvard University	Percentage shift from illicit to legal market for current adult users Percentage change over time in current prices of marijuana
Regulatory oversight	Washington State Institute for Public Policy (WSIPP) MDPH	State regulation costs State regulation revenue Number of infractions per RMD per year
Law enforcement	Massachusetts Executive Office of Public Safety and Security (EOPSS)	Number of misdemeanor arrests Number of misdemeanor convictions Number of incarcerations Number of inmates on supervised release (parolees/probationers) Percentage change in misdemeanor arrests Percentage change in misdemeanor convictions Percentage change in incarcerations Percentage change in supervised release Costs of employee training on cannabis impaired driving
Public health and safety	Colorado Department of Public Health Massachusetts Bureau of Substance Abuse Services	Suicide estimates (used in supplementary analyses) Marijuana Tax Cash Fund expenditures Cost associated with substance use disorder treatment

MDPH = Massachusetts Department of Public Health; RMD = registered marijuana dispensary.

Secondary Data Sources

We augmented information from the literature and key informant interviews with analyses of a number of secondary data sources. To estimate taxable sales from marijuana, we required information on marijuana pricing. We extracted this information from three websites that aggregate crowd-sourced information on marijuana pricing (as of December 2017): Budzu and PriceofWeed (which enables users to submit information on the location where they purchased marijuana and on the price, amount, and quality of the marijuana purchased) and a document hosted on Google Sheets called Dispensary Sheet (which displays information about the price of marijuana for each amount sold at Massachusetts dispensaries). Because retail marijuana sales are not yet legal, information on the current price per gram of dried flower marijuana from these sites may contain a combination of prices in the illicit market and those in the medical market. We also used data supplied by MDPH to identify the median price of medical marijuana sold in registered marijuana dispensaries (RMDs) in Massachusetts (see Appendix D).

We obtained data on the prevalence of current marijuana use from a combination of the MBHS Task 1 survey of the general population in Massachusetts; the 2015 National Survey on Drug Use and Health (NSDUH, based on national estimates because Massachusetts-specific detailed data were unavailable at the time of the analysis¹²); and the 2015 Behavioral Risk Factor Surveillance System (BRFSS) of Massachusetts residents.^{13,14} For adolescent marijuana use prevalence, we obtained estimates from the 2015 Massachusetts Youth Risk Behavior Surveillance System (YRBSS) survey of 9th through 12th grade students,¹⁵ the 2015 Massachusetts Youth Health Survey (YHS) of middle and high school students,¹⁶ and 2015–2016 NSDUH estimates.¹⁷

We gathered estimates of changes in regulatory costs and revenue attributable to retail legalization from CCC, MDPH, Washington, and Colorado budgets. Given that the CCC is expected to take over regulatory oversight of the medical marijuana program from MDPH, the increase in start-up costs for Massachusetts fiscal year (FY) 2018 were based on the difference between the CCC budget estimate¹⁸ and projected FY 2017 costs from the MDPH's Medical Marijuana Trust Fund Annual Report.¹⁹ Thereafter, for FY 2019 and FY 2020, we inflated CCC and MDPH projections of costs to account for the expected growth in the number of RMDs in operation (estimated to be 26 by the end of FY 2018, 40 by the end of FY 2019, and 123 by the end of FY 2020, based on data posted by MDPH on the current status of all registered marijuana dispensaries and applications through January 12, 2018²⁰). We also translated recurring marijuana-related law enforcement costs incurred in Washington (based on the I-502 Fiscal Impact Statement²¹) and public safety costs incurred in Colorado²² to Massachusetts' projected costs on a per capita basis.

Sources of regulatory revenue within the first two years of legalization include marijuana dispensary application fees and fines collected for infractions or deficiencies. To

¹² <https://www.samhsa.gov/samhsa-data-outcomes-quality/major-data-collections/reports-detailed-tables-2015-NSDUH>.

¹³ https://www.cdc.gov/brfss/annual_data/annual_2015.html.

¹⁴ We defined respondents who indicated past-month or past-30 day marijuana use as current users. We chose past-month use because it was the most contemporary use option available, and because we identified only minor differences (less than 5%) between past-month and past-year users in 90% of records.

¹⁵ <https://nccd.cdc.gov/youthonline/App/Results.aspx?LID=MA>.

¹⁶ <https://www.mass.gov/files/documents/2016/09/vp/youth-health-risk-report-2015.pdf>.

¹⁷

<https://www.samhsa.gov/data/sites/default/files/NSDUHsaePercents2016/NSDUHsaePercents2016.pdf>.

¹⁸ https://www.mass.gov/files/documents/2017/11/08/CNB_Budget_Request_FINAL.pdf.

¹⁹ <https://www.mass.gov/files/documents/2017/03/zs/mmj-annual-trust-fund-report-2017.pdf>.

²⁰ <https://www.mass.gov/service-details/massachusetts-medical-use-of-marijuana-program-snapshot>.

²¹ <http://www.vote.wa.gov/guides/2012/I-502-Fiscal-Impact.html>.

²² <https://drive.google.com/file/d/0B0TNL0CtD9wXdjFWWUhlMm5TMjQ/view>.

estimate regulatory revenue, we inflated FY 2017 projections from MDPH's Medical Marijuana Trust Fund Annual Report, as described above for the start-up costs, to reflect the growth in RMDs. We also included estimated fines that the CCC will collect for infractions in FY 2019 and FY 2020. Though CCC fines can be as high as \$25,000 per deficiency, we assumed an average fine of \$1,000 (in line with Group 2 regulatory marijuana fines in Washington²³) and assumed five deficiencies per RMD per year (based on conversations with MDPH). We did not factor in additional licensing revenue because, based on our analysis of data from MDPH on the current status of all registered marijuana dispensaries and applications through January 12, 2018, we do not expect to see a substantial increase in the number of RMD applications in the two-year study period compared to current application rates.

Finally, several secondary data sources informed our estimates of public health effects of adult use legalization: treatment admission data from the 2011 and 2016 Massachusetts Treatment Episode Data Set (TEDS)²⁴ and the Massachusetts Budget and Policy Center, data on suicides from the 2015 Centers for Disease Control and Prevention National Vital Statistics System statistics on Massachusetts, traffic fatality statistics from the 2015 Fatality Analysis Reporting System (which were compiled by the MBHS Task 2 team), and 2016 data on the number of opioid-related deaths from MDPH.

To translate estimates from other states to Massachusetts, we used data from the U.S. Census microdata (Ruggles, Genadek, Goeken, Grover, & Sobek, 2017) and the 2015 American Community Survey 5-Year Estimates (United States Census Bureau, 2015) on Massachusetts population size and demographics.

MBHS Task 1 Survey

We analyzed data from the Massachusetts general population adult survey, administered as part of MBHS Task 1 by the University of Massachusetts' Donahue Institute, to obtain estimates of the prevalence of marijuana use, the number of regular versus heavy users of marijuana, and use by mode of consumption. All estimates were based on weighted frequencies that were generated using SAS PROC SURVEYSELECT (SAS version 9.4).

Our estimate of prevalence of current marijuana use came from a question on use of marijuana or hashish at least once within the past 30 days. We calculated the prevalence of use statewide (based on all individuals surveyed) and combined this information with data on the prevalence of use obtained from the NSDUH and BRFSS surveys to obtain a range of plausible values that fed into our models. We also estimated the number of regular versus heavy users of marijuana in Massachusetts based on definitions in the literature that rely on the number of days of marijuana use in

²³ <http://apps.leg.wa.gov/wac/default.aspx?cite=314-55-525>.

²⁴

https://www.samhsa.gov/data/sites/default/files/TEDS2011St_Web/TEDS2011St_Web/TEDS2011St_Web.pdf (Tables 2.1 and 2.2) and <https://www.dasis.samhsa.gov/webt/quicklink/MA16.htm>.

the past month (Kilmer et al., 2013). We calculated the number of individuals surveyed who used marijuana between 1 and 20 days in the past month (defined as regular users) and how many used marijuana 21 days or more in the past month (defined as heavy users). Finally, we examined modes of consumption and found that the clear majority of users (95%) consume marijuana as a dried flower product (by smoking or vaporization)—either alone or in combination with other modes of consumption (such as by eating it, dabbing it, or applying it topically or sublingually). We therefore based our pricing of marijuana on price per gram of dried flower product.

In addition, we estimated prevalence of marijuana use at the city or town level using data collected in the MBHS Task 1 survey by respondents' five-digit ZIP code. Because ZIP codes tend to span multiple cities, we used a two-part approach to allocate respondents to a single city or town, based on MassGIS data on city and town boundaries.²⁵ (1) we associated each ZIP code to the city or town that contained the majority of the ZIP code boundary, and (2) if no city contained the majority of the ZIP code boundary, we used the town or city that contained the geographic center of the ZIP code. We then calculated the prevalence of current marijuana use in each city or town for cities and towns with at least 15 MBHS Task 1 survey respondents (to ensure we had sufficient data to produce a valid estimate); for the remaining municipalities, we estimated the prevalence by averaging the current marijuana use prevalence estimates from the national NSDUH and Massachusetts-specific BRFSS surveys.

Statistical Modeling

Our model estimates the fiscal impacts of shifting from a medical marijuana to a broader adult use program within the first two years after retail sales begin. We also include start-up costs and revenue. Our modeling consists of three models:

- (1) A *main* model, which includes primary measures that we hypothesize are major drivers of economic impacts to the state and for which there is strong evidence to inform estimates: sales tax revenue, regulatory oversight costs and revenue, and reductions in marijuana-related law enforcement activities
- (2) A *supplemental* model, which adds secondary impacts on public health, public safety, and income tax revenue for which the evidence is less definitive or immediate than those domains included in the main model
- (3) A *local* model, which estimates local tax revenue for each city or town in Massachusetts (assuming the maximum local tax rate of 3%)

We first calculated measure-specific revenue or savings and measure-specific costs or losses by multiplying various input estimates (for example, to calculate marijuana sales revenue, we multiplied the estimated number of marijuana users by the average grams of marijuana used per day by the average price per gram of marijuana). To do so, we combined information on pre-legalization baseline measures (such as the number of marijuana users) with estimates of the post-legalization change (such as the percentage

²⁵ <https://docs.digital.mass.gov/dataset/massgis-data/zip-codes-5-digit-here0navteq-0>.

change in the number of marijuana users). We next estimated the precision of our post-legalization estimates, and finally tested the sensitivity of the findings to key assumptions. To calculate the post-legalization fiscal impact of marijuana legalization for metrics in our model, we defined a range of plausible values using information from the literature, stakeholder interviews, secondary data sources, and the MBHS Task 1 survey. We then used Monte Carlo simulation—a method that is useful when there is inherent uncertainty about model inputs—to randomly draw a value from the range for each metric and then use that value to calculate the overall impact estimate. This process of randomly drawing values from the range was repeated 1,000 times, each time resulting in a different value, to generate a probability distribution of values for the impact metric. This simulated distribution was then used to calculate a 95% confidence interval—a low and high range that indicates precision—around the impact estimate. To obtain an overall impact estimate of adult use legalization, we summed together measure-specific (for example, sales tax revenue from marijuana purchases by adults considered heavy users, adults considered regular users, and adolescents) for each domain included in the model.²⁶ In Table 2, we summarize baseline and projected values for each input in our models (see Appendix C Table C.1 for detailed information on the variables and data sources used to construct each measure). In the Limitations section, we indicate the measures we excluded from our model because we lacked sufficient data or causal evidence for their inclusion.

²⁶ Because we produce a distribution of outcome values for each level of impact (measure, domain, and model), the average value for a summed outcome will not exactly equal the sum of the average components that fed into it (for example, the sum of the individual measures used to calculate sales tax revenue does not exactly equal the total impact of the sales tax revenue domain); however, the differences are small.

Table 2. Main and Supplemental Model Input Values

Measure	Baseline	Projected	Difference	(%)
Main model				
Domain: Sales and business tax revenue				
Sales tax revenue from marijuana purchases				
Number of adolescent users age 17 or younger	158,892	158,616	-276	(-0.2%)
Number of regular users age 18 or older ^a	318,797	394,896	76,099	(23.9%)
Number of heavy users age 18 or older ^a	150,436	150,436	0	(0%)
Sales tax revenue from beer	\$72,830,435	\$69,271,226	-\$3,559,209	(-4.9%)
Business income tax revenue from dispensaries	0	\$40,501,857	\$40,501,85	(n.a.)
			7	
Domain: Regulatory oversight				
Costs over two years	\$41,927,099	\$43,706,042	\$1,778,944	(4.2%)
Revenue over two years	\$112,728,59	\$114,914,00		
	9	6	\$2,185,407	(1.9%)
Domain: Law enforcement				
Marijuana related				
Arrests	240	84	-156	(-65%)
Convictions	159	57	-102	(-63.9%)
Incarcerations	40	14	-26	(-65%)
Parolees and probationers	122	43	-79	(-64.8%)
Averted mortality due to traffic fatalities ^b	306	274	-32	(-10.6%)
Employee training on cannabis impaired driving	\$0	\$655,000	\$655,000	(n.a.)
Supplemental model				
Domain: Public health				
MassHealth prescription drug expenditures	\$459,769,13	\$452,684,07		
	5	3	-\$7,085,063	(-1.5%)
Substance abuse treatment admissions				
Cannabis	2,840	3,387	547	(19.2%)
Opioid	3,956	3,498	-458	(-11.6%)
Averted mortality ^b				
Opioid-related deaths	1,990	1,633	-357	(-17.9%)
Suicides, males age 20-29	76	67	-9	(-11.2%)
Suicides, males age 30-39	77	68	-9	(-11.2%)
Worker productivity				
Full-time equivalent dispensary jobs	110	617	507	(461.0%)
Hourly earnings, males age 20-29	\$15.60	\$15.21	0	(-2.5%)
Females age 50+ with a qualifying medical marijuana condition, employed full time	90,584	99,093	8,509	(9.4%)
Males age 50+ with a qualifying medical marijuana condition, hours worked/week	41.7	43.8	2	(5%)

Sources: Mathematica's analysis of impacts of legalized adult use of marijuana in Massachusetts using estimates from the literature, key stakeholder interviews, and primary and secondary data sources. See Appendix C Table C.1 for data sources used to inform these estimates.

Note: Baseline values are for Massachusetts fiscal year 2018 (before retail sales begin), while projected value are for fiscal year 2020 (the second year of retail sales).

^a Regular users are those who consume marijuana between 1 and 20 days per month; heavy users are those who consume marijuana 21 or more days per month (Kilmer et al., 2013).

^b These numbers are also used to estimate income tax revenue from averted mortality in the supplemental model.

n.a. = not applicable.

Sensitivity Analyses for State-Level Models

We conducted two analyses to examine the sensitivity of our results. The first involves the number of current marijuana users in Massachusetts. In our primary analysis, we used the NSDUH and BRFSS population surveys to establish a range (8.6% to 12.1%) for the prevalence of current marijuana use in Massachusetts. In a sensitivity analysis, we expanded the high end of the range to 20.1%, based on the MBHS Task 1 survey estimate. It is unclear why the estimate of use prevalence was substantially higher in the MBHS Task 1 survey than in existing population surveys. On the one hand, because the NSDUH and BRFSS surveys were conducted prior to adult use legalization, they may have underreported marijuana use, which is a recognized problem in surveys targeting illegal substance use (Harrison, Martin, Enev, & Harrington, 2007). Because the MBHS Task 1 survey was conducted after the referendum to legalize retail marijuana was passed in Massachusetts, it may have captured more honest reporting that captures true Massachusetts-specific consumption patterns. However, it should be noted that the rate of consumption reported in Colorado in the 2014–2015 NSDUH—which was conducted after legalization—was still only 17%. On the other hand, because the MBHS Task 1 survey response rate was low (roughly 20% of individuals who were mailed a survey completed the survey), it is not clear how representative MBHS Task 1 survey estimates are of the general adult population in Massachusetts and whether self-reporting bias affected the estimates obtained. In our sensitivity check, we examined what effect using the MBHS Task 1 survey consumption estimate as the high end of the range had on our overall impact estimate.

In our second sensitivity analysis, we set all impacts based on the medical marijuana literature to zero, given the possibility that these impacts might have already been realized when Massachusetts implemented the medical marijuana program. In our primary analysis, we assume that the expansion from the medical marijuana to the adult use of marijuana regime will generate similar impacts as the expansion from no legalization to the medical marijuana regime. However, while far from conclusive, the limited evidence of the impacts from the expansion from medical to retail legalization are small or statistically insignificant (Dills, Goffard, & Miron, 2016, 2017). In this sensitivity analysis, we take the conservative view that there are no behavioral impacts generated from the shift from the medical to adult use regimes beyond consumers switching from the black market to legal retail market. In other words, we do not anticipate any impacts of adult use legalization on the likelihood or frequency of marijuana consumption, nor do we anticipate any impacts on public health outcomes explored in the supplemental model, such as alcohol or opioid consumption, or economic impacts from increased labor force participation of older adults. The results from this sensitivity analysis can therefore serve as a lower bound of the expected fiscal impact of marijuana legalization in Massachusetts.

Local Analyses

To estimate fiscal impacts to local governments, we projected the revenue that cities and towns would collect from local taxes imposed on retail marijuana sales during the

first two years of adult use legalization. Unlike our main model, the local model does not factor in costs associated with adult use legalization (such as increased training and law enforcement costs that are anticipated at the local level) because of the high level of uncertainty associated with these costs, coupled with a lack of local-level data to inform such estimates. To estimate revenue, we assumed a local tax rate of 3% (the maximum local tax) in all cities and towns with an RMD expected to open within the first two years of retail marijuana sales. We applied this rate to the projected number of marijuana purchases, calculated using the prevalence of current marijuana use assumed in our state-level models (defined to range from 8.6% to 12.1%, based on the NSDUH and BRFSS surveys), which was assumed to be consistent across all cities and towns. In a sensitivity analysis, we used local-level prevalence estimates that were informed by the MBHS Task 1 survey for cities and towns with at least 15 individuals surveyed. We assumed that marijuana users in cities and towns without a projected RMD would purchase marijuana from the nearest city or town with an RMD. Based on the locations of RMDs expected to open within the two-year study period, we expect that individuals in the majority of cities and towns (n = 337) will reside within 10 miles of an open RMD and that all individuals in Massachusetts will reside within 20 miles of an RMD. Finally, in the primary local analysis, we assumed that 50% to 80% of marijuana users would shift from purchasing their marijuana in the illicit market to purchasing from RMDs, based on information from the Washington State Institute of Public Policy (WSIPP) and a stakeholder interview. In a sensitivity analyses, we set the shift to 50% and 80% to examine the effect on the results.

Results

Main Model Impacts

Our main model included changes in the following primary measures: sales tax revenue (from marijuana purchases among adults with regular and heavy use and among adolescents using marijuana purchased from RMDs); business income tax revenue from RMDs (which we estimated by applying an 8% business tax rate to our estimate of gross revenue, excluding business-related expenses); regulatory costs and revenue; and marijuana-related law enforcement activities (related to decreases in arrests, convictions, incarcerations, and parolees/probationers). Based on our main model, we estimate that marijuana legalization will result in a net two-year fiscal contribution of \$215.8 million (Figure 1 and Table 3). The majority of this gain (70%, amounting to \$150.3 million) will come from sales tax revenue, followed by RMD business tax revenue (28%, amounting to \$60.1 million); about 2% will come from savings due to reduced law enforcement needs to police illegal marijuana use; and less than 1% will come from regulatory revenue—largely because we estimate that Massachusetts will spend about the same amount to regulate marijuana sales and production (\$1.8 million) as it will receive in application fees and violation fines from marijuana dispensaries (\$2.2 million). Based on the probability distribution generate from the Monte Carlo simulation, we estimate a 95% confidence interval of \$95.7 to \$405.9 million around our main model impact estimate.

Sales tax revenue was driven largely by marijuana purchases anticipated by adults categorized as heavy users (we estimate these consumers are responsible for \$89.8 million of the \$150.3 million expected in new sales tax revenue). Additional sales tax revenue comes from: adults categorized as regular marijuana users (\$23.3 million); adolescents who consume marijuana that was purchased by adults from RMDs (\$14.6 million); tourist purchases (\$14.4 million), which we assumed would comprise between 7% and 12% of total tax revenue, based on estimates from Light et al. (2016) and Cooper et al. (2016); and new adult users (\$7.7 million), whose use of marijuana begins after the commencement of retail sales. As a result of retail marijuana sales, we also forecast a \$3.6 million reduction in sales tax revenue from beer sales over the study period. The majority of law enforcement savings are realized through reductions in law enforcement costs related to vehicular crashes that result in fatalities (\$3.8 million) and in the number of marijuana-related incarcerations (\$1.4 million).

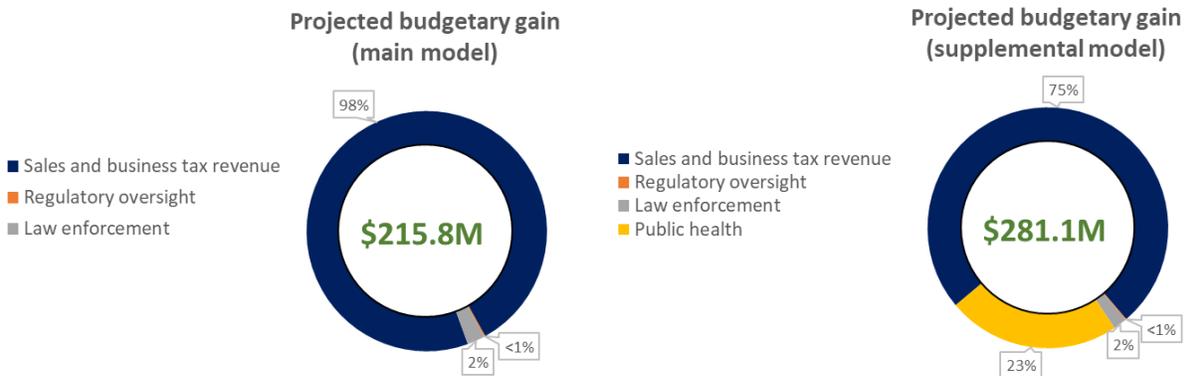
Supplemental Model Impacts

Our supplemental model included changes in the following health-related measures estimated with less certainty: income tax revenue (mainly as a result of increases in worker productivity among adults age 50 or over, coupled with extra years of life due to averted mortality), decreased MassHealth spending on prescription drugs replaced with marijuana, decreased spending on opioid addiction treatment, increased spending on cannabis addiction treatment, and state-level savings due to averted deaths. With respect to averted deaths, the evidence from the medical marijuana literature suggests a decrease in traffic fatalities (Anderson, Hansen, & Rees, 2013; Santaella-Tenorio, Mauro, Wall, Kim, & Martins, 2017), which would decrease legal costs to the state, along with a decrease in suicides among males ages 20 to 39 (Anderson, Rees, & Sabia, 2014), which would decrease state spending on related medical costs. Adding these measures to our main model increased our projected budgetary gain by \$65.3 million, and yielded a total impact estimate of \$281.1 million (Table 3). Across all domains, estimated changes in sales and business tax revenue represent approximately 75% of all economic and fiscal impacts, while revenue and savings as a result of public health effects account for an additional 23%; regulatory oversight and law enforcement fiscal impacts together constitute less than 5% of estimated impacts. The 95% confidence interval around the secondary model impact estimate was \$98.4 million to \$528.3 million.

When we examine projected revenue or savings (without factoring in projected costs or losses), the single largest contributor is sales tax revenue for marijuana purchases at RMDs by heavy adult users, followed by marijuana-related business income tax revenue (Appendix C Figure C.1). We also estimate substantial income tax revenue from gains in worker productivity (\$54.4 million). In particular, we project growth in hours worked among men over age 50 (\$46.7 million) and in full-time employment among women over age 50 (\$20.9 million) who have a debilitating medical condition (such as chronic back pain or depression) that is well-controlled with marijuana. Retail marijuana legalization is estimated to reduce mortality from suicides, vehicular crashes, and opioid-related deaths; together, these could increase income tax revenue by \$1.1 million and reduce state public health spending by \$0.7 million.

When we look at costs or losses (data not shown), we project that a reduction in average hourly earnings as a result of marijuana addiction or dependence will reduce state income tax revenue by \$12.5 million. We also estimate a loss of \$3.6 million in alcohol sales taxes because of substitution effects (whereby individuals purchase marijuana in lieu of alcohol). The estimated impact on state spending for substance abuse treatment is minimal, composed of reduced spending on opioid addiction treatment (\$1.0 million) that is offset by increased spending on cannabis addiction treatment (\$1.1 million).

Figure 1. Estimated Two-Year Impacts of Legalizing Adult Use of Marijuana



Sources: Mathematica’s analysis of impacts of legalized adult use of marijuana in Massachusetts using estimates from the literature, key stakeholder interviews, and primary and secondary data sources. See Appendix C Table C.1 for data sources used to inform these estimates.

Note: Each model sums the estimated changes in revenue or savings and the estimated costs or losses associated with the domains in the legend. Changes were projected within the first two years of retail sales, and include start-up costs associated with migrating from a medical marijuana program to a broader adult use marijuana program. Percentages sum to more than 100% due to rounding.

Table 3. Estimated Two-Year Impacts by Model and Domain

Model	Estimated net gain in revenue	Range (95% confidence interval)
Main model	\$215,750,686	\$95,740,066 –
Sales and business tax	\$210,431,454	
Sales tax revenue	\$150,308,182	
Business income tax	\$60,123,273	
Law enforcement	\$5,055,969	
Regulatory oversight	\$406,463	
Supplemental model	\$281,054,592	\$98,400,908 –
Public health	\$65,303,906	\$2,660,843 – \$122,382,655
Individual income tax	\$57,400,988	
State spending on	\$7,764,492	

Sources: Mathematica’s analysis of impacts of legalized adult use of marijuana in Massachusetts using estimates from the literature, key stakeholder interviews, and primary and secondary data sources. See Appendix C Table C.1 for data sources used to inform these estimates.

Note: The sum across domains may not equal the overall estimate because of random variation in the simulations. The range is based on the 95% confidence interval around the model estimate.

Sensitivity of Impacts

In our first sensitivity analysis, in which we increased the upper end of the range of plausible values for prevalence of current marijuana use to include the MBHS Task 1 survey estimate, our main model impact estimate increased by 38% (from \$215.8 million to \$298.8 million), and our supplemental model estimate increased by 29% (from \$281.1 million to \$364.1 million). In our second sensitivity analysis, in which we adjusted all impacts derived from the medical marijuana literature to zero, our main model estimate decreased by only 8% (to \$143.9 million), but our supplemental model estimate (which included a number of public health measures informed by the medical marijuana literature) decreased by 28% (to \$201.4 million).

Local Impacts

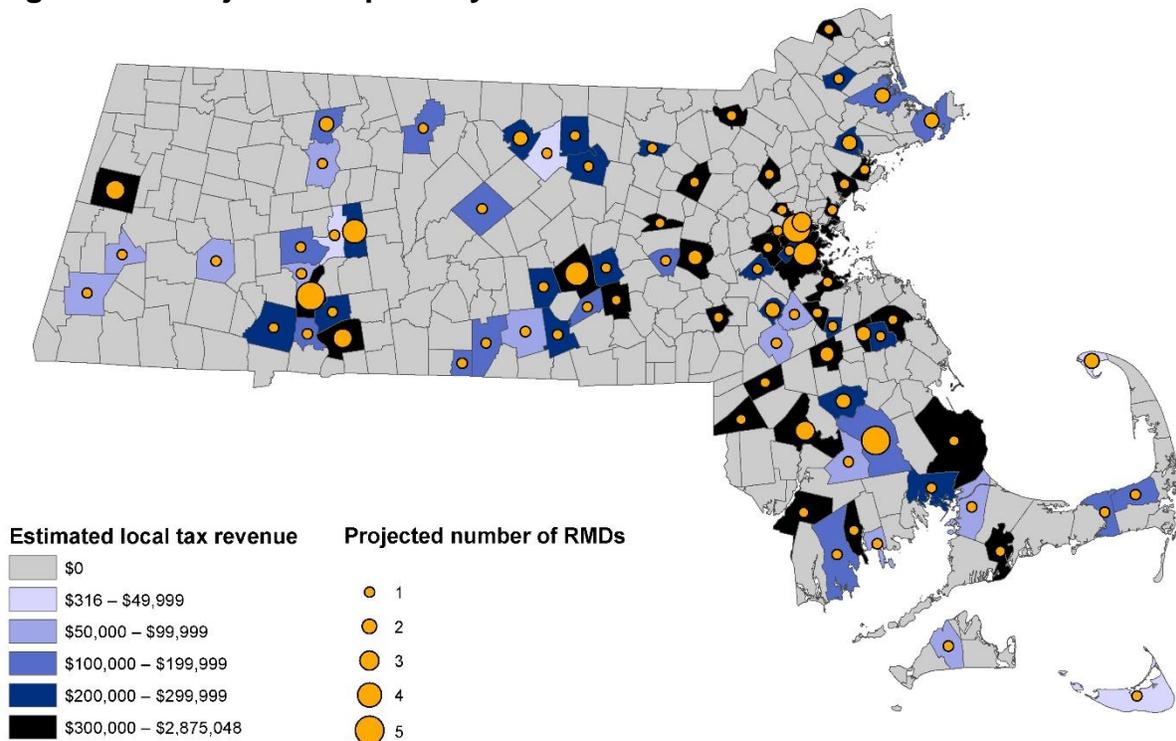
In Figure 2, we show our estimated two-year local tax revenue, assuming a 3% local tax rate, along with information on the projected number of RMDs expected per city or town. With some exceptions, local tax revenue is generally higher on the coast and lower in the western part of the state. In Table 4, we summarize estimated local tax revenue by city or town density, defined using the methodology of Pozzi and Small (2005) as rural (≤ 100 people/km²); suburban low, medium, and high density (100–500 people/km², 500–1,000 people/km², and 1,000–10,000 people/km², respectively); and urban ($> 10,000$ people/km²). As expected, revenue is highest in dense regions, though there is considerable fluctuation in tax revenue projections among the 51 high-density suburban cities and towns (see Appendix C Table C.3 for detailed results). Both sets of results are

restricted to the 83 cities and towns in which an RMD is expected to be open within the first two years of retail marijuana sales.

In Appendix C Figure C.2, Table C.2, and Table C.3, we show how local revenue estimates would change if RMDs were open in all cities and towns across Massachusetts, such that marijuana users would no longer travel to nearby cities or towns to purchase marijuana. For some of the 83 cities and towns included in the primary analysis—particularly those that will be more isolated from other RMDs in the state—local tax revenue estimates dropped dramatically (for example, from about \$992,000 in Burlington to about \$108,000).

In the sensitivity analysis in which we used local-level marijuana use prevalence estimates that were informed by the MBHS Task 1 survey (which were available mostly for urban and high-density suburban cities and towns), our estimate of local tax revenue increased by 215% for urban cities (to almost \$1.3 million) and by 20% for high-density suburban cities (to about \$288,000). And in the sensitivity analysis in which we specified that the percentage shift in marijuana purchases from the illicit market to RMDs would be exactly 50% or 80% (instead of 65%, which we derived for the primary analysis based on the range of 50% to 80%), our median revenue estimates decreased and increased, respectively, by 18% for all density categories.

Figure 2. Estimated Two-Year Local Tax Revenue by City or Town with a Registered Marijuana Dispensary



Sources: Mathematica’s analysis of impacts of legalized adult use of marijuana in Massachusetts using estimates from the literature, key stakeholder interviews, and primary and secondary data sources. See Appendix C Table C.1 for data sources used to inform these estimates.

Note: The figure includes estimates only for cities and towns in which a marijuana dispensary is projected to be open within the first two years of marijuana retail sales; no rural areas (< 100 people/km²) are expected to have open dispensaries. Appendix C Table C.2 provides estimates assuming RMDs are open in all Massachusetts cities and towns within the first two years of legalization. See Appendix C Table C.3 for estimates by city or town.

Table 4. Estimated Two-Year Local Tax Revenue by Density Category

City or Town Type	Number of Cities or Towns	Two-Year Local Tax Revenue		
		Median	Minimum	Maximum
Suburban, low density (100–500	6	\$72,835	\$60,801	\$144,385
Suburban, medium density (501–	10	\$63,272	\$20,872	\$170,209
Suburban, high density (1,001–10,000	51	\$243,144	\$68,139	\$991,873
Urban (> 10,000 people/km ²)	16	\$582,899	\$233,498	\$2,875,048

Sources: Mathematica’s analysis of impacts of legalized adult use of marijuana in Massachusetts using estimates from the literature, key stakeholder interviews, and primary and secondary data sources. See Appendix C Table C.1 for data sources used to inform these estimates.

Note: The table includes only cities and towns in which a marijuana dispensary is projected to be open within the first two years of marijuana retail sales; no rural areas (< 100 people/km²) are expected to have open dispensaries. Appendix C Table C.2 provides estimates assuming RMDs are open in all Massachusetts cities and towns within the first two years of legalization. See Appendix C Table C.3 for estimates by city or town.

Discussion

We estimate that the legalization of adult use of marijuana will result in an increase of approximately \$215.8 million to the Massachusetts state budget over the first two years of retail sales, largely as a result of sales and excise taxes collected on retail marijuana purchases. Although our model includes fiscal impacts of legalization due to a number of domains, most are miniscule compared to increases expected from sales and business tax revenue. The increase will largely be a result of retail purchases made by adults with heavy use—defined as consuming marijuana an average of 21 days or more each month. New business income tax revenue from marijuana dispensaries will also be a major contributor, as will increases in income tax revenue (primarily due to increased worker productivity among adults over age 50 who are able to control debilitating medical ailments with marijuana). When we included measures calculated with less certainty (because of either a lack of data or an uncertain time frame within which impacts could occur), we estimate that the state may see an additional \$65.3 million added to its budget. This increase would mainly come from added individual income tax revenue from worker productivity gains in older adults able to control serious ailments with marijuana.

Our estimate of tax revenue is heavily influenced by assumptions about the number of current marijuana users in Massachusetts. Because previous population surveys (used to inform our main model estimates) yielded a lower estimate of prevalence of use than the MBHS Task 1 survey, our main model estimate may be conservative. However, because we assumed that changes seen when moving from medical marijuana sales to retail marijuana sales could be as high as moving from no legal marijuana sales to medical marijuana sales, our fiscal estimates could also be somewhat higher than may be realized.

A strength of our analytic approach is that the Monte Carlo simulation factors the uncertainty of inputs into the model estimates; that is, we were able to incorporate plausible ranges of values for inputs to not overstate their certainty. The combination of uncertain inputs leads to substantial uncertainty in the estimated impact of adult use legalization on the state budget, as indicated by the wide confidence interval around the estimate. As more studies are published on the impacts of adult use legalization, the ranges of estimates from the literature will be better defined and our impact estimates will become more precise.

The results of our model should be interpreted in the context of Massachusetts-specific information, such as the proposed regulatory framework, tax regime, and existing medical marijuana program. Below, we provide additional details on the assumptions and implications of our approach with respect to the four domains included in our analysis: sales tax revenue, regulatory oversight, law enforcement, and public health. We also compare how our estimate of the fiscal impact of adult use of marijuana legalization compares with previous impact estimates (generated from the Massachusetts Department of Revenue [DOR] and in other states with legalized use) and discuss limitations of our approach.

Sales Tax Revenue

We project fiscal impacts within a two-year window starting at the commencement of retail marijuana sales, but it is important to note that the revenue generated is heavily weighted toward the tail end of the two-year period. Indeed, in other states that have implemented retail marijuana sales for at least two years (Colorado, Washington, and Oregon), 66% to 77% of sales tax revenue collected within the first two years was generated in the second year (Colorado DOR, 2018; Oregon DOR, n.d.; Washington State LCB, n.d.), and the data suggest that sales tax revenues are likely to increase substantially after consumers, suppliers, and regulators adjust to the new regime.²⁷ Based on data from these states, we assumed that about 70% of the two-year estimate of sales tax revenue would be collected from Massachusetts RMDs in the second year of sales. This translates to an estimated \$61.6 million collected in the first year and

²⁷ Alaska collected less tax revenue from legal marijuana in its second year of sales than in its first. However, Alaska differs from other states that have legalized marijuana—including Massachusetts—in many respects, including the fact that they tax marijuana by plant weight, rather than through a tax rate applied to retail sales (<http://tax.alaska.gov/programs/programs/reports/Annual.aspx?60000&Year=2017>). Therefore, we excluded Alaska when reviewing the experiences of states that allow marijuana sales.

\$154.2 million in the second year of retail sales. It is important to note we cannot claim with certainty that spending on marijuana represents new spending rather than a shift from other recreational options like spending on alcohol. Similarly, income tax revenue from new dispensary jobs may represent transfers from other industries. As a result, it is possible that some amount of tax revenue generated by legalization may be offset by a reduction in tax revenue elsewhere.

Our methodology for estimating change in tax revenue attributable to marijuana legalization differs from other models in two major respects. First, we did not factor in changes in the price of marijuana over time because it is particularly difficult to know the rate at which prices will change within the first two years of legalization (Hunt & Pacula, 2017). Instead, we estimated a single, average price of marijuana during the study period based on crowd-sourced data and data from RMDs. We also did not link marijuana prices to sales volumes—that is, examine the price elasticity of demand—because doing so compounds this uncertainty.²⁸ Instead, we estimated changes in demand using marijuana use quantities derived from the literature and MBHS Task 1 survey results, coupled with changes in use behavior derived from the growing body of evidence from states that have legalized marijuana use.

Second, we did not account for expected increases in revenue related to the establishment and growth of the broader marijuana industry. Several previous studies attempted to quantify these macroeconomic impacts, with mixed results; one study concluded that previous analyses underestimate or overestimate impacts by up to 300% (Light, Orens, Rowberry, & Saloga, 2016). However, it is likely that the development of a novel industry will generate some amount of tax revenues from businesses that grow, manufacture, or test marijuana and stimulate growth among traditional businesses that supply or interact with this new market.

Our model also assumed a steady growth rate in medical marijuana patients (based on current growth trajectories) that would be unchanged after retail sales begin. Because medical marijuana is untaxed in Massachusetts, it may be more attractive to new marijuana consumers once retail sales begin. Accordingly, it is possible that the initiation of retail sales could actually increase the rate of growth in medical marijuana use. However, we did not model this scenario.

Whenever possible, we benchmarked our estimates against other sources. For example, we found that the median price per gram of dried flower marijuana (\$13.70) based on crowdsourced data for Massachusetts was nearly identical to the median price per gram sold by RMDs for medical use (\$13.30). Also, based on stakeholder interviews, we estimated that the price of marijuana during the two-year study period will be roughly 75% of the current price. The prices also align with data from other sources, which suggest that post-legalization prices in other states have fallen roughly 20% per year (Committee on Foreign Affairs and International Trade, 2018). Finally, data on

²⁸ This approach is similar to the one used by Cooper, Johnston, & Segal (2016) to model the economic impact of marijuana sales in California.

marijuana use frequency from the MBHS Task 1 survey align with data from the 2015–2016 NSDUH survey of Massachusetts residents in that both suggest that approximately two-thirds of current marijuana users are “regular” users based on their use frequency being between 1 and 20 days per month, and the remaining one-third are “heavy” users based on a use frequency of 21 or more days per month. The sources also indicate that regular users average 7 use days per month, and heavy users average approximately 29 use days per month.

Estimates of the average amount of marijuana consumed per day of use among current marijuana users were inconsistent between the MBHS Task 1 survey and the literature. To estimate dollars spent per day of marijuana use, we derived dollars spend in the past month on the average number of days marijuana was used in the past month—both of which were estimated using the MBHS Task 1 survey. We then divided this by the average price per gram of marijuana to estimate the average number of grams used per day. Our calculations yielded an average daily use of: 0.17 grams consumed by regular users and 0.32 grams consumed by heavy users. By contrast, estimates from Kilmer et al. (2013) were much higher: 0.67 grams and 1.6 grams, respectively. One explanation for the difference is that marijuana potency may have increased between 2013 and 2017, such that consuming fewer grams now achieves the same effect as in 2013. Another possibility is that our estimate of the price per gram of marijuana was inaccurate. Our estimate combines information on black market and RMD pricing. If MBHS Task 1 survey respondents paid less per gram than we estimated, this would then result in higher estimates that may be more in line with Kilmer et al. (2013). To account for the uncertainty in average marijuana grams consumed each day of use, we varied the model estimate for use between the MBHS Task 1 survey estimate and the estimate from Kilmer et al. (2013).

Regulatory Oversight

Our model suggests that within the first two years of retail sales, the cost of regulatory oversight will be offset by revenue generated from application fees and fines collected by the CCC. However, our analyses of regulatory costs incurred by other states that have legalized retail sales show a great deal of variability in the cost of regulating marijuana, even after accounting for differences in population size and number of RMDs. In Washington (which has approximately 100 marijuana dispensaries²⁹), we estimated total regulatory costs to be \$52,638 per dispensary per year, whereas in Colorado (which has approximately 371 marijuana dispensaries³⁰), the corresponding estimate was \$31,945. There are, however, notable differences in regulatory operations between states. For example, following legalization of adult use of marijuana in Washington in 2012, the state did not create a new regulatory agency but rather incorporated cannabis regulation under the state’s LCB. Given that Massachusetts will have a separate regulatory body—the CCC—rather than incorporating cannabis regulation under the state’s LCB, Massachusetts may incur additional costs not included

²⁹ Based on data from <https://www.marijuanadoctors.com/medical-marijuana-dispensaries/WA>.

³⁰ Based on data from <https://www.colorado.gov/pacific/enforcement/med-licensed-facilities>.

in the estimates from Washington. Additionally, at the time of legalizing retail marijuana, Washington did not have a robust medical marijuana law or medical dispensaries prior to the legalization of adult use of marijuana (even though medical marijuana had been legal in Washington since 1998).³¹ Medical marijuana became more formally regulated in Washington in 2015, requiring a second wave of regulatory work to incorporate medical use under the LCB.

Data from Washington show that 55% of regulatory costs incurred within the first two years of legalization were associated with rulemaking, licensure, and enforcement; spending on health and social service programs accounting for another 38% of costs. In Washington, these costs totaled \$105,250 per year after start-up, whereas in Colorado, the cost ranged from \$164,634 to \$172,031 per year. In our model, we considered as regulatory costs any recurring law enforcement activities at the state and local level, including employee blood testing for individuals suspected of driving under the influence as well as administrative, legal, and judicial costs associated with suspended or revoked licenses. We estimated these costs by translating the range of estimates from Washington and Colorado to Massachusetts on a per capita basis.

Because of a lack of data, we did not attempt to factor regulatory costs at the local level into our model. We learned through a stakeholder interview that local governments in Washington struggled to keep up with ongoing regulatory changes, which required several staff dedicated to monitoring these changes. Although local governments initially absorbed start-up costs required to regulate businesses locally, eventually the fees they collected on licenses ended up covering the costs of regulating businesses locally. Based on information from the CCC,³² we anticipate that the Marijuana Regulation Fund that the CCC establishes could cover much of the costs of education and prevention as well as municipal police training. The expert we interviewed also indicated that the main factor differentiating local regulatory costs in Washington, from one city to another, is whether the city focuses on marijuana production or on retail sales. For producers (which are largely located in rural areas), primary costs involve odor and environmental issues surrounding waste disposal and wastewater. For retailers (which are more concentrated in urban areas), age compliance and traceability have been major sources of concern that have added costs. Also, rural towns—which were more likely to ban marijuana retail sales—incurred costs associated with lawsuits by businesses wanting to open an RMD.

Law Enforcement

Our modest projected reductions of law enforcement costs reflect a two-thirds decrease in marijuana arrests in the years preceding legalization of retail sales.³³ Because few

³¹ <https://www.doh.wa.gov/YouandYourFamily/Marijuana/MedicalMarijuana/LawsandRules/HistoryinWashington>.

³² <https://malegislature.gov/Laws/GeneralLaws/PartI/TitleXV/Chapter94G/Section14>.

³³ According to data supplied to the authors by the Massachusetts Department of Corrections, the number of cases charged with a marijuana governing offense declined from 975 in 2010 to 336 in 2014.

people currently enter the criminal justice system for marijuana offenses, further decreases in incarcerations will have little effect on statewide expenditures. However, this estimate is subject to a few limitations. First, it is difficult to obtain reliable data on individuals charged with marijuana offenses who are also charged with other, more serious crimes. It is possible that sentence lengths assigned to this group will be reduced when marijuana sales are legally permitted, further reducing costs. Second, some law enforcement officials in Massachusetts and elsewhere are skeptical of findings that marijuana legalization reduces vehicular crashes and express concern about increases in the incidence of driving under the influence of marijuana (Migoya, 2017; stakeholder interview). If these concerns are borne out, traffic fatalities will represent an increase rather than a decrease in expenditures. Also, there may be other benefits that manifest from reducing the proportion of the population incarcerated for marijuana-related crimes. However, such benefits are challenging to quantify, given a lack of evidence, and they may take longer than two years to be realized.

With respect to impaired driving, our model included an estimated decrease in motor vehicle fatalities attributed to adult use of marijuana legalization. There is some evidence of increases in THC blood concentrations among drivers after adult use legalization that could also contribute to increases in non-fatal motor vehicle crashes. For example, a report from Washington that analyzed trends over time before and after adult use of marijuana legalization found that the proportion of drivers testing positive for THC was fairly constant before and immediately after adult use legalization took effect, but that beginning approximately 9 months after adult use legalization took effect, the proportion began to increase substantially at a rate of 9.7% per year (Tefft, Arnold, & Grabowski, 2016). In addition, the law enforcement communities in Colorado and Washington have expressed anecdotal concerns that marijuana is increasing both fatal- and non-fatal motor vehicle crashes (Migoya, 2017). Because these studies did not meet our causal evidence guidelines, we did not include estimates from them in our model.

Finally, although our model factored in a start-up cost of \$655,000 in Massachusetts (based on stakeholder input) for Drug Recognition Expert and Advanced Roadside Impaired Driving Enforcement officer training, data from Washington indicate that the costs could be much higher. The Washington State Patrol spent \$2.1 million on employee training on cannabis impaired driving, which accounts for 77% of the increase in law enforcement costs attributed to marijuana legalization within the first five years. Additional costs may be incurred for driving campaigns and other public safety messaging.

Public Health

Our supplemental model added projected fiscal impacts due to public health impacts of legalizing adult use of marijuana. We estimate that revenue and savings related to public health impacts will account for about 23% of the total budgetary gains projected because of legalization, based on our supplemental model. The added budgetary gain in our supplemental model mainly comes from projected increases in worker

productivity (which would generate increases in individual income tax revenue) among older adults with debilitating medical conditions that are well controlled with marijuana (Nicholas & Maclean, 2016). We assumed that these productivity gains would be fully realized within the first two years of retail sales; if they span longer than two years, model estimates would need to be proportionally reduced. We also suspect that some of the productivity gains projected may have already been realized by the medical marijuana population. However, when we adjusted the population to which we applied the impact estimate (by subtracting out older medical marijuana patients, based on data from MDPH), our impact estimate decreased by only 8% for older women and 4% for older men.

Other public health savings (for example, due to reduced spending by the state on the MassHealth program to cover prescription drugs for fee-for-service beneficiaries) are expected to account for only 3% of the supplemental model estimate. Decreases in Medicaid prescription drug spending, estimated by Bradford and Bradford (2017), were based on treatment for medical conditions that medical marijuana is used to treat, including depression and psychosis. That is, we project that some individuals will use marijuana in lieu of prescription medications to treat these conditions. Because of a lack of information on how spending might change because of marijuana legalization, our model did not account for changes in spending associated with inpatient, outpatient, or emergency treatment—it was limited to prescription spending alone. It is also important to note that our model projects impacts only out to two years, and that the health effects associated with marijuana use could have a much longer latency, possibly taking decades before the full extent of benefits or harms would be seen.

Projected savings of roughly \$980,000 due to decreases in opioid addiction treatment were offset by projected spending amounting to \$1.1 million due to increases in cannabis addiction treatment. For both sets of costs, we focused only on the costs of treatment admissions incurred by the state. However, many individuals with drug addiction or dependence do not seek treatment; instead, costs incurred by the state government for these individuals may be related to costs associated with overdoses and emergency room visits. Because of a lack of data, we did not incorporate non-treatment costs related to addiction/dependence in our model. Likewise, when we factored in the measure related to reductions in opioid-related deaths into our model, we only accounted for increases in income tax revenue. We did not account for reductions in other costs that may be incurred for opioid-related deaths, such as the cost of ambulatory treatment (which is covered by MassHealth) or mortuary costs (which are expected to be relatively small, given a \$1,500 cap on MassHealth coverage for these costs).

In our model, expected decreases in suicides among males age 20 to 39 accounted for less than 1% of expected public health savings. Although there have been anecdotal concerns that legalization of adult use of marijuana has led to an increase in suicides in Colorado and Washington, neither the literature nor state-level data we examined reflect this measure. For example, the most recent Colorado Violent Death Reporting System report noted an increase in the suicide rate in 2014 and 2015, although there were no

statistically significant changes observed during this time period (Jamison, Mintz, Herndon, & Bol, 2017). Using data from this report, we calculated the change in suicide rate from the three-year period before legalization (2011–2013) to the two year-period after legalization (2014–2015) and noted a 6.25% increase in suicides over this time period. However, given that the report itself found that these changes were not statistically significant, we did not include them in our model.

Comparison with Previous Estimates

Our model included estimates of sales tax revenue as well as revenues and costs realized in other domains. Although there are no comparable estimates of projected revenues and costs related to business and income tax revenue, public health, and criminal justice costs, we discuss below the differences between our estimates of projected sales tax revenue and estimates from other states and from the DOR for Massachusetts.

Our estimate of taxable retail marijuana sales was \$748.7 million (\$224.6 million in the first year and \$524.1 million in the second). The second year estimate amounts to \$745 per adult user, which is similar to second year estimates from Oregon (\$675) and Washington (\$818) but is substantially lower than the second year estimate for Colorado (\$1,128).³⁴ Differences across the states could be attributed to any or all of the following:

- *Differences in the speed at which the programs are fully implemented.* Because it takes new dispensaries one to two years to be fully operational in Massachusetts, retail marijuana sales may be limited at first, particularly in areas without RMDs. However, the fact that Massachusetts has a well-established medical marijuana program (unlike Washington at the time of retail marijuana legalization) and can learn from the experiences of other states with legalized use could hasten implementation of the adult use program.
- *Differences in tourist sales volumes.* Marijuana purchases by tourists to Colorado may have been substantially higher in the first two years of legalized adult use than they will be in Massachusetts. Colorado was the first state to implement an adult use program, and even now most of its bordering states do not have medical marijuana programs. By contrast, Massachusetts borders two other states that have legalized adult marijuana use (Vermont and Maine), and all its bordering states have medical marijuana programs.

³⁴ For comparability with retail sales estimates in Massachusetts and in Oregon (calculated by dividing revenue estimates from <http://www.oregon.gov/DOR/programs/gov-research/Pages/research-marijuana.aspx> by the 17% tax rate), we converted total sales revenue (which included medical plus retail sales) in Colorado (<https://www.colorado.gov/pacific/revenue/colorado-marijuana-sales-reports>) and Washington (Washington State LCB dashboard, n.d.) to retail sales revenue by subtracting the percentage of revenue due to medical sales, which we assumed would be equal to the percentage of total marijuana users (<https://www.samhsa.gov/data/sites/default/files/NSDUHsaeSpecificStates2016A/NSDUHsaeSpecificStates2016.htm>) that are medical users (<https://www.mpp.org/issues/medical-marijuana/state-by-state-medical-marijuana-laws/medical-marijuana-patient-numbers/>).

- *Differences in tax rates.* The 17% sales plus excise tax rate in Massachusetts is lower than the rate of almost 30% in Colorado, and much lower than the rate of 44% in Washington. As a result, more of the total demand in Massachusetts could be met by RMDs, as opposed to the illicit market, resulting in higher sales volumes per user compared with other states.

Our estimate of projected revenue collected through the maximum 20% tax rate in Massachusetts (assuming a maximum local tax of 3%) is substantially lower than estimates produced by the Massachusetts DOR. We estimate that the state will collect almost \$105 million in tax revenue from \$524 million in sales; the DOR report projects roughly \$205 million in revenue from \$1.1 billion in sales, after adjusting to the increase from a 12% to a 20% tax rate (Joint Committee on Marijuana Policy, 2017).^{35,36} However, the difference is reduced by roughly one-third when we compare the DOR estimate to the estimate from our sensitivity analysis that uses the Task 1 survey's estimate of prevalence of current marijuana use.

The difference between our estimate and the DOR estimate is primarily due to the DOR applying per capita sales estimates from the third year of legalized use in Colorado and Washington (which saw nearly 50% and 70% increases between years two and three, respectively) to the second year of legalization in Massachusetts, believing that Massachusetts will have a shorter implementation period because the state has the benefit of learning from the experiences in Colorado and Washington. If Massachusetts second-year sales approach third-year levels from those other states, our model may underestimate this component of the fiscal impacts of legalization. However, as noted above, the speed at which dispensaries are approved to begin retail sales across the state could limit the extent to which the state is able to ramp up sales. In Massachusetts, we project that the revenue in the second year will more than double the first year's revenue. For comparison, the second year's revenue nearly doubled in Colorado and nearly tripled in Washington compared to the first year.

Limitations

Our models exclude a number of potential impacts of adult use of marijuana legalization that do not have supporting casual evidence to link the impact to marijuana laws and policies. For example, we do not have sufficient information on the impacts of legalization on a number of public health outcomes, including spending related to

³⁵ The Massachusetts DOR estimates \$128 million of tax revenue collected on \$1.07 billion in taxable sales based on a 12% total tax rate (including sales, excise, and local taxes). In a sensitivity analysis, they estimate \$237 million of tax revenue collected on \$1.018 billion in sales assuming a total tax rate of 23.25%. Based on these estimates, we calculate that the DOR estimate would be roughly \$205 million in tax revenue with a total tax rate of 20%.

³⁶ The Massachusetts DOR report cites two reports with estimates that were lower than its own – a Tax Foundation Report (estimating \$747 million in taxable sales based on a 15% tax rate) and a study by the Massachusetts Special Senate Committee on Marijuana (estimating \$500 million in taxable sales) – and a third report with an estimate that was similar to their own (a study by ArcView Market Research estimating \$1.07 billion in taxable sales in 2020).

emergency room or urgent care visits and the prevalence of low birth weight, obesity, tobacco use or nicotine dependence, and non-fatal vehicular crashes. We also did not include changes in spending related to poison control center costs because the changes were estimated to be quite small. It is possible that adult use of marijuana legalization could lead to changes in marijuana consumption that would in turn affect these and other public health outcomes. Finally, we did not factor in potential spending related to increases in energy or water use related to marijuana growth and production. Second, because literature on adult use of marijuana is sparse, our model estimates rely mainly on the medical marijuana literature. That is, we assumed that changes observed when migrating from no legal marijuana to medical marijuana would be similar to changes observed when migrating from medical marijuana to adult use of marijuana. Ideally, causal impacts taken from the literature would reflect the impacts of shifting from a medical marijuana market to a market that includes medical and broader adult use of marijuana. The limited studies on adult use of marijuana legalization have not found statistically significant impacts from the expansion of medical marijuana to broader adult use. However, a recently published study provides additional evidence that supports our strategy to use medical marijuana impact estimates. Powell, Pacula, & Jacobson (2015) found that the relationship between medical marijuana laws and the reduction in opioid deaths is influenced by the type of medical marijuana laws that states implemented. They found that opioid deaths decreased only in states in which marijuana dispensaries were easily available to patients. In Massachusetts, the medical marijuana program is more tightly regulated than in other states, and the state has fewer legal medical marijuana patients per 1,000 people than many other states that have legalized medical marijuana. Moreover, the number of qualifying conditions for medical marijuana use in Massachusetts is fewer than those in other states and does not include chronic pain, which is a qualifying condition in 13 of the states that have legalized medical marijuana (ProcCon, 2017). Therefore, the impact of marijuana legalization in Massachusetts may not be fully realized prior to adult use legalization, and the impact of medical marijuana policies in states with more liberal guidelines may provide insight into the expected impact of adult use legalization in Massachusetts. A third potential limitation of our model is that we assumed that each input metric acts independently of other metrics; therefore, we did not account for the correlations between metrics in our model. It is analytically feasible to incorporate relationships between metrics into the impact estimates, for example, by factoring in the price elasticity of demand to see how marijuana use changes as pricing changes.

Finally, it is not clear whether the impacts projected from our model will sustain beyond the two-year time frame. Most of the impacts in our model can be considered one-time (but not necessarily immediate) shifts as a result of legalization. For example, we may not expect marijuana-related arrests to further decrease beyond the two-year time frame, nor do we expect the start-up costs of establishing the regulatory framework to persist. However, impacts on consumption and associated public health outcomes may take longer to realize because they depend on market prices, the accessibility of dispensaries, and other factors that are associated with a high degree of uncertainty.

Directions for Future Research

The MBHS provides a valuable baseline understanding of the impacts of legalization in Massachusetts and serves as a benchmark to improve the implementation of marijuana legalization in other states. In this report, we synthesize information from a number of sources to provide projections that serve as a reference to compare to the actual experience in Massachusetts as the program unfolds. Such a comparison can be used to better understand the factors driving the fiscal impacts of adult use of marijuana and to project future impacts beyond the first two years of legalization. Our analysis should also help the state and localities anticipate what resources may be needed to roll out the adult use program.

References

- Anderson, D. M., Hansen, B., & Rees, D. I. (2013). Medical marijuana laws, traffic fatalities, and alcohol consumption. *The Journal of Law and Economics*, *56*(2), 333-369. <https://doi.org/10.1086/668812>
- Anderson, D. M., Hansen, B., & Rees, D. I. (2015). Medical marijuana laws and teen marijuana use. *American Law and Economics Review*, *17*(2), 495-528. <https://doi.org/10.1093/aler/ahv002>
- Anderson, D. M., Rees, D. I., & Sabia, J. J. (2014, December). Medical marijuana laws and suicides by gender and age. *American Journal of Public Health*, *104*(12), 2369-2376. <http://doi.org/10.2105/AJPH.2013.301612>
- Aos, S., Phipps, P., Barnoski, R., & Lieb, R. (2001). *The comparative costs and benefits of programs to reduce crime. Version 4* (Washington State Institute of Public Policy). Retrieved from Education Resources Information Center website: <https://eric.ed.gov/?id=ED453340>
- Bachhuber, M. A., Saloner, B., Cunningham, C. O., & Barry C. L. (2014). Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999–2010. *JAMA Internal Medicine*, *174*(10), 1668–1673. <http://doi.org/10.1001/jamainternmed.2014.4005>
- Birnbaum, H. G., White, A. G., Schiller, M., Waldman, T., Cleveland, J. M., & Roland, C. L. (2011). Societal costs of prescription opioid abuse, dependence, and misuse in the United States. *Pain Medicine*, *12*(4), 657–667. <http://doi.org/10.1111/j.1526-4637.2011.01075.x>
- Blincoe, L. J., Miller, T. R., Zaloshnja, E., & Lawrence, B. A. (2015, May). *The economic and societal impact of motor vehicle crashes, 2010 (revised)* (National Highway Traffic Safety Administration, DOT HS 812 013). Retrieved from U.S. Department of Transportation website: <https://crashstats.nhtsa.dot.gov/Api/Public/ViewPublication/812013>
- Bradford, A. C., & Bradford, W. D. (2017). Medical marijuana laws may be associated with a decline in the number of prescriptions for Medicaid enrollees. *Health Affairs (Project Hope)*, *36*(5), 945–951. <http://doi.org/10.1377/hlthaff.2016.1135>
- Choo, E. K., Benz, M., Zaller, N., Warren, O., Rising, K. L., & McConnell, K. J. (2014). The impact of state medical marijuana legislation on adolescent marijuana use. *Journal of Adolescent Health*, *55*(2), 160–166. <http://doi.org/10.1016/j.jadohealth.2014.02.018>
- Chu, Y.W.L. (2015). Do medical marijuana laws increase hard-drug use? *The Journal of Law and Economics*, *58*(2), 481–517. <http://doi.org/10.1086/684043>
- Colorado Department of Revenue. (2018). Marijuana tax data. Retrieved from Colorado State website: <https://www.colorado.gov/pacific/revenue/colorado-marijuana-tax-data>
- Committee on Foreign Affairs and International Trade, Senate of Canada, Ottawa, Canada (2018, March 22). Designing cannabis supply to promote temperance. (Testimony of Mark Kleiman) Retrieved from Marron Institute website: https://marroninstitute.nyu.edu/uploads/content/Designing_Cannabis_Supply_to_Promote_Temperance_-_Kleiman_Sep_2017.pdf

- Cooper, W., Johnston, E., & Segal, K. (2016, April). *The economic impacts of marijuana sales in the state of California* (ICF International white paper). Retrieved from ICF International website: <https://www.icf.com/resources/white-papers/2016/economic-impact-of-marijuana-sales-in-california>
- Darnell, A. J., & Bitney, K. (2017). *I-502 evaluation and benefit-cost analysis: Second required report* (Washington State Institute for Public Policy, 17-09-3201). Retrieved from Washington State Institute for Public Policy website: http://www.wsipp.wa.gov/ReportFile/1670/Wsipp_I-502-Evaluation-and-Benefit-Cost-Analysis-Second-Required-Report_Report.pdf
- Dills, A., Goffard, S., & Miron, J. (2016, September 16). *Dose of reality: The effect of state marijuana legalizations* (CATO Institute Policy Analysis No. 799). Retrieved from the CATO website: <https://object.cato.org/sites/cato.org/files/pubs/pdf/pa799.pdf>
- Dills, A. K., Goffard, S., & Miron, J. (2017). *The effects of marijuana liberalizations: Evidence from monitoring the future* (National Bureau of Economic Research No. w23779). <http://doi.org/10.3386/w23779>
- Friese, B., Grube, J. W., & Moore, R. S. (2013). Youth acquisition of alcohol and drinking contexts: An in-depth look. *Journal of drug education*, 43(4), 385-403. <http://dx.doi.org/10.2190/DE.43.4.f>
- Harrison, L. D., Martin, S. S., Enev, T., & Harrington, D. (2007, May). *Comparing drug testing and self-report of drug use among youths and young adults in the general population*. Retrieved from Buckley's Renewal Center website: <http://www.buckleysrenewalcenter.com/wp-content/uploads/2012/02/drugtest.pdf>
- Hasin, D. S., Sarvet, A. L., Cerdá, M., Keyes, K. M., Stohl, M., Galea, S., & Wall, M. M. (2017). U.S. adult illicit cannabis use, cannabis use disorder, and medical marijuana laws: 1991–1992 to 2012–2013. *JAMA Psychiatry*, 74(6), 579–588. <http://doi.org/10.1001/jamapsychiatry.2017.0724>
- Hasin, D. S., Wall, M., Keyes, K. M., Cerdá, M., Schulenberg, J., O'Malley, P. M., Galea, S., Pacula, R., & Feng, T. (2015). Medical marijuana laws and adolescent marijuana use in the USA from 1991 to 2014: Results from annual, repeated cross-sectional surveys. *The Lancet Psychiatry*, 2(7), 601–608. [http://doi.org/10.1016/S2215-0366\(15\)00217-5](http://doi.org/10.1016/S2215-0366(15)00217-5)
- Hunt, P., & Pacula, R. L. (2017). Early impacts of marijuana legalization: An evaluation of prices in Colorado and Washington. *Journal of Primary Prevention*, 38(3), 221–248. <http://doi.org/10.1007/s10935-017-0471-x>
- Jamison, E., Mintz, S., Herndon, K., & Bol, K. (2017, October). Suicide in Colorado, 2011-2015: A summary from the Colorado Violent Death Reporting System. *Health Watch*, 102. Retrieved from Colorado State website: https://www.colorado.gov/pacific/sites/default/files/CHED_CoVDRS_HealthWatch_Suicide-in-Colorado-2011-2015-Colorado-Violent-Death-Reporting-System_1017%20.pdf
- Joint Committee on Marijuana Policy* (2017, March 20) (Testimony of Commissioner Michael Heffernan, Massachusetts Department of Revenue).

- Kilmer, B., Caulkins, J. P., Midgette, G., Dahlkemper, L., MacCoun, R. J., & Pacula, R. L. (2013). *Before the grand opening: Measuring Washington State's marijuana market in the last year before legalized commercial sales*. Retrieved from RAND Corporation website: https://www.rand.org/pubs/research_reports/RR466.html
- Light, M., Orens, A., Rowberry, J., & Saloga, C.W. (2016, October). *The economic impact of marijuana legalization in Colorado*. Retrieved from Marijuana Policy Group website: <http://mjpolicygroup.com/pubs/MPG%20Impact%20of%20Marijuana%20on%20Colorado-Final.pdf>
- Marijuana Policy Project. (2018, February 26). *Medical marijuana patient numbers*. Retrieved from MPP website: <https://www.mpp.org/issues/medical-marijuana/state-by-state-medical-marijuana-laws/medical-marijuana-patient-numbers/>
- Migoya, D. (2017, August 27). Traffic fatalities linked to marijuana are up sharply in Colorado. Is legalization to blame? *The Denver Post*. Retrieved from <https://www.denverpost.com/2017/08/25/colorado-marijuana-traffic-fatalities/>
- Nicholas, L. H. & Maclean, J. C. (2016). *The impact of medical marijuana laws on the labor supply and health of older adults: Evidence from the Health and Retirement Study* (National Bureau of Economic Research, No. w22688). Retrieved from Social Science Research Network website: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2846904
- Oregon Department of Revenue. (n.d.). *Oregon marijuana tax statistics*. Retrieved from Oregon State website: <http://www.oregon.gov/dor/programs/gov-research/pages/research-marijuana.aspx>
- Powell, D., Pacula, R. L., & Jacobson, M. (2015). *Do medical marijuana laws reduce addictions and deaths related to pain killers?* (National Bureau of Economic Research, No. w21345). <http://dx.doi.org/10.3386/w21345>
- Pozzi, F., & Small, C. (2005, June). Analysis of urban land cover and population density in the United States. *Photogrammetric Engineering & Remote Sensing*, 71(6), 719–726. Retrieved from American Society for Photogrammetry and Remote Sensing website: https://www.asprs.org/wp-content/uploads/pers/2005journal/jun/2005_jun_719-726.pdf
- ProCon. (2016, March 3). *Number of legal medical marijuana patients*. Retrieved from ProCon website: <https://medicalmarijuana.procon.org/view.resource.php?resourceID=005889>
- ProCon. (2017, November 20). *29 legal medical marijuana state and DC: Laws, fees, and possession limits*. Retrieved from ProCon website: <https://medicalmarijuana.procon.org/view.resource.php?resourceID=000881Massachusetts>
- Ruggles, S., Genadek, K., Goeken, R., Grover, J., & Sobek, M. (2017). *Integrated public use microdata series: Version 7.0* [Data file]. Minneapolis: University of Minnesota.
- Russell, E. M., Cook, K. R., Gold-Alexander, D., Rollins, R. S., Wilson, P., Wong, L., & Cerasoli, R. (2017, December 27). *Alcoholic Beverages Control Commission of Massachusetts: Task force report*. Retrieved from Massachusetts State website: https://www.mass.gov/files/documents/2017/12/28/Alcohol%20Task%20Force%20Report_0.pdf

- Sabia, J., & Nguyen, T. T. (2016, March). *The effect of medical marijuana laws on labor market outcomes* (IZA Discussion Paper, 9831). Retrieved from IZA Institute of Labor Economics website: <http://ftp.iza.org/dp9831.pdf>
- Santaella-Tenorio, J., Mauro, C., Wall, M., Kim, J., & Martins, S. (2017). Reductions in traffic fatalities rates across states with operational dispensaries of marijuana. *Drug and Alcohol Dependence*, 171. <http://doi.org/10.1016/j.drugalcdep.2016.08.500>
- Shepard, D. S., Gurewich, D., Lwin, A. K., Reed, G. A., Jr., & Silverman, M. M. (2015). Suicide and suicidal attempts in the United States: Costs and policy implications. *Suicide and Life-Threatening Behavior*, 46(3), 352–362. <https://doi.org/10.1111/sltb.12225>
- Tefft, B. C., Arnold, L. S., & Grabowski, J. G. (2016). *Prevalence of marijuana use among drivers in fatal crashes: Washington, 2010-2014*. Retrieved from AAA Foundation for Traffic Safety website: <https://aaafoundation.org/prevalence-marijuana-use-among-drivers-fatal-crashes-washington-2010-2014/>
- United States Census Bureau. (2015). *B01001: Sex by age. 2011–2015 American Community Survey*. Washington, DC: U.S. Census Bureau, American Community Survey.
- Washington State Liquor and Cannabis Board. (n.d.). *Marijuana dashboard*. Retrieved from Washington State website: <https://data.lcb.wa.gov/stories/s/%20WSLCB-Marijuana-Dashboard/hbnp-ia6v/>
- Wen, H., Hockenberry, J., & Cummings, J. R. (2014). *The effect of medical marijuana laws on marijuana, alcohol, and hard drug use* (National Bureau of Economic Research, No. w20085). <http://doi.org/10.3386/w20085>
- Wen, H., Hockenberry, J. M., & Cummings, J. R. (2015). The effect of medical marijuana laws on adolescent and adult use of marijuana, alcohol, and other substances. *Journal of Health Economics*, 42, 64–80. <http://doi.org/10.1016/j.jhealeco.2015.03.007>
- Wide Open Eats. (2017). *How much each state pays for a case of beer on average*. Retrieved from Wide Open Eats website: <http://www.wideopeneats.com/much-case-beer-costs-state/>

Appendix

Appendix A

DPH Statewide Survey Tool



Massachusetts Survey of Health and Social Behavior: Marijuana Baseline Health Study

Please have the adult in your household (18 years or older) who is a Massachusetts resident and had the most recent birthday complete this survey. We do not mean the oldest person. We mean the person who had a birthday last. While every question is important to our study, this survey is completely voluntary and you can skip any question.

If you would prefer to complete this survey online, please go to:

<http://TinyURL.com/HealthSurveyMA>

Instructions for Completing the Booklet

This booklet contains several types of questions. Each question should be answered only about yourself, not anyone else in your household.

- For some questions, you answer the question by marking a box, like this (please mark only one box, unless directed otherwise):

Yes
 No

- For some questions, you answer the question by filling in one number per box, like this:

0 9

- You will sometimes be instructed to skip one or more questions. In this example, if your choice is 'No', you skip to question 10; otherwise, you continue to the next question.

Yes
 No → **Go To Question 10**

Thank you for taking the survey. Please check one box for each question unless the directions ask you to do otherwise.

Household Demographics

1. How many adults age 18 years or older live in your household? (Please fill in the number.)

Number of adults

2. How many children under 18 years old live in your household?

Number of children

3. Many people only live in Massachusetts for part of the year. Do you live in Massachusetts for 6 or more months out of the year?

Yes
 No

4. In what year were you born?

Year

5. What is your gender?

Male
 Female
 Other

6. Are you Hispanic or Latino?

Yes
 No

7. Which one or more of the following would you say is your race? (Check all that apply.)

White or Caucasian
 Black or African American
 Asian
 Native Hawaiian or Other Pacific Islander
 Native American or Alaskan Native
 Some other race



Draft

8. What is the highest degree or level of school you have completed?

- Never attended school or only attended kindergarten
- Grades 1 through 8
- Grades 9 through 11
- Regular high school diploma or GED
- Some college credit, but less than one year of college credit
- One or more years of college credit, no degree
- Associate degree
- Bachelor's degree
- Master's degree
- Professional degree beyond a bachelor's degree
- Doctorate degree

9. What is your annual household income from all sources?

- Less than \$15,000
- \$15,000 – \$29,999
- \$30,000 – \$49,999
- \$50,000 – \$99,999
- \$100,000 – \$149,999
- \$150,000 or more

10. What is the zip code where you currently live?

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Zip Code

11. What type of healthcare coverage do you have?

(Check all that apply.)

- Private commercial or group plan (for example, an HMO or PPO through an employer)
- Medicare
- Medicaid
- Commonwealth Care Program (Health Connector)
- Indian Health Services
- Veterans Affairs (VA)
- No Health Insurance
- Other plan

12. Do you own the place where you currently live, pay rent, or something else?

- Own
- Rent
- Something else

Opinion

In 2016, Massachusetts voters legalized marijuana for recreational use. We are trying to understand how this change may affect the attitudes and behaviors of Massachusetts residents.

13. Do you believe that marijuana should be legal for recreational use in Massachusetts?

- Yes
- No

14. How much do you think people risk harming themselves (physically or in other ways) if they use marijuana regularly?

- No risk
- Slight risk
- Moderate risk
- Great risk

Social Behaviors

Now we will ask about some of your social behaviors. Please remember that this survey is private and confidential. Each question should be answered only about you, not anyone else in the household.

Alcohol Consumption

The next set of questions is about alcohol. One drink of alcohol is equal to a 12-ounce beer, a 5-ounce glass of wine, or a drink with one shot of liquor.

15. During the past 30 days, did you have at least one drink of any alcoholic beverage such as beer, wine, a malt beverage, or liquor?

- Yes
- No → Go To Question 20

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16. During the past 30 days, how many days per week did you have at least one drink of any alcoholic beverage?

Days per week

17. During the past 30 days, about how much money did you spend on alcohol in total? (Only include alcohol that you consumed. Do not include alcohol that you purchased for other purposes, such as gifts or storage.)

\$, Dollars

18. During the past 12 months, how many times were you treated in an emergency room or urgent care facility for any reason related to alcohol use?

- 0 times
- 1 time
- 2–3 times
- 4–5 times
- 6 or more times

19. During the past 30 days, how many times have you driven a car or other motor vehicle while you were under the influence of alcohol?

- 0 times
- 1 time
- 2–3 times
- 4–5 times
- 6 or more times

20. During the past 30 days, how many times did you ride as a passenger in a car or other motor vehicle when the driver was under the influence of alcohol?

- 0 times
- 1 time
- 2–3 times
- 4–5 times
- 6 or more times

Marijuana

The next set of questions is about marijuana. People sometimes call this cannabis, weed, pot, grass, ganje, hashish, hash, or other terms. Please remember that this survey is private and confidential. Each question should be answered only about you, not anyone else in the household.

21. During the past 30 days, did you use marijuana or hashish at least once?

- Yes
- No → Go To Question 28

22. During the past 30 days, on how many days did you use marijuana or hashish?

Days

23. During the past 30 days, which of the following purposes did you use marijuana for? (Check all that apply.)

- Recreational use (Non-medical)
- Medical use (Prescribed by a qualified physician)
- Medical use (Not prescribed by a qualified physician)

24. During the past 30 days, how did you use marijuana? (Check all that apply.) Did you:

- Smoke it (in a joint, bong, pipe, or blunt)
- Eat it (in brownies, cakes, cookies, or candy)
- Drink it (in tea, cola, alcohol)
- Vaporize it (in an e-cigarette-like vaporizer)
- Dab it (using butane hash oil, wax, or concentrates)
- Apply it topically on the skin (using cannabis oil, cannabis ointment/lotion, or topical cannabis salve)
- Use rectal cannabis suppositories
- Use sublingual (under-the-tongue) uptake products (dissolvable strips, sublingual sprays, or medicated lozenges)



25. During the past 30 days, about how much money did you spend on marijuana in total? (Only include marijuana that you consumed. Do not include marijuana that you purchased for other purposes, such as gifts or storage.)

\$, Dollars

26. During the past 12 months, how many times were you treated in an emergency room or urgent care facility for any reason related to marijuana use?

- 0 times
- 1 time
- 2-3 times
- 4-5 times
- 6 or more times

27. During the past 30 days, how many times did you drive a car or other motor vehicle when you were under the influence of marijuana or hashish?

- 0 times
- 1 time
- 2-3 times
- 4-5 times
- 6 or more times

28. During the past 30 days, how many times did you ride as a passenger in a car or other motor vehicle when the driver was under the influence of marijuana or hashish?

- 0 times
- 1 time
- 2-3 times
- 4-5 times
- 6 or more times

Other Substances

The next set of questions is about substance use other than alcohol or marijuana, both prescription drugs used for non-medical purposes and other substances. Please remember that this survey is private and confidential. Each question should be answered only about you, not anyone else in the household.

"Non-medical" prescription drug use means using it to get high or experience pleasurable effects, see what the effects are like, or use with friends.

29. During the past 30 days, did you use any of the following drugs? (Check all that apply.) Did you use . . .

- Cocaine or Crack
- Heroin
- Non-medical use of anti-anxiety drugs such as Sedatives/Tranquilizers/Anxiolytics or sleeping drugs such as Benzodiazepines/Barbituates
- Non-medical use of prescription opioids such as Oxycodone/OxyContin, Hydrocodone/Vicodin, Morphine, Methadone, Fentanyl
- Other (Please write in your answer):

None → Go To Question 34

30. During the past 30 days, on how many days did you use the drug or drugs that you indicated in the previous question?

Days

31. During the past 30 days, about how much money did you spend on drugs, either prescription drugs or other substances, in total? (Only include drugs that you consumed. Do not include drugs that you purchased for other purposes, such as gifts or storage.)

\$, Dollars



Appendix B

DPH Patient Survey Tool



**MASSACHUSETTS DEPARTMENT
OF PUBLIC HEALTH**

MARIJUANA BASELINE HEALTH STUDY

MEDICAL USE OF MARIJUANA PATIENT SURVEY

Dear Participant,

Thank you for taking the time to complete this survey on medical use of marijuana.

The purpose of this survey is to better understand the patterns of use and perceptions among medical use of marijuana patients in Massachusetts. The information you provide will help to inform the safe use and implementation of marijuana legalization in Massachusetts. This survey will ask questions about your use of marijuana and other substances. There is a small risk that some of the questions may make you feel uncomfortable.

Filling out this survey is completely voluntary. You do not have to answer any question you do not want to. You can stop this survey at any time. Choosing to not participate in this survey will not affect your access to marijuana or any other related service.

All information that you provide is confidential. You will be asked to provide your unique Registration Number that is visible on your Program ID card to complete the survey. You will not be asked to provide your name or any other identifying information. Your responses will not be tied back to you in a way that can be identified. Your name or any other identifying information will not be tied to your responses.

This research study has been reviewed by the Massachusetts Department of Public Health (MDPH) Institutional Review Board (IRB). The Commissioner of the Massachusetts Department of Public Health has approved this study in accordance with Massachusetts General Law c. 111 s. 24A. This law protects the confidentiality of all information collected for this study. This law states that the information we collect is not available as a public record. It may not be used as evidence in any legal proceedings. This means that individually identifying information about you will not be shared with anyone outside the study team. It will not be used for any purpose other than for this study.

This survey will include questions on the following topics:

Basic information about you (your age, your racial identity, and what county you live in)
Your current and past experiences regarding the use of marijuana for medical purposes
Your current and past experiences using other drugs

This survey should take between 20-30 minutes to complete.

There are no direct benefits to all participants as a result of participating in this survey. However, as an incentive for your participation, you will be asked at the end of this survey if you would like to be entered into a drawing to win a gift card worth \$100, \$250, or \$500. If you would like to participate, your identifier will be entered into a pool with other participants for the chance to win a gift card. If your identifier is chosen as a winner you will be contacted through email to receive your gift.

**If you have any questions about this survey, please contact [REDACTED]
[REDACTED] or at MBHS@state.ma.us.**

For more information about your rights as a research participant, please contact the MDPH IRB at (617) 624-5621.

Thank you again for your time today.

Demographics

1. What is your age?

18 to 25

26 to 35

36 to 50

51 to 64

65+

2. What is your gender?

Male

Female

Other, please specify: _____ *

Refuse to answer

3. Are you currently pregnant?

Yes

No

Don't Know/Not sure

Refuse to Answer

4. Are you currently breastfeeding?

Yes

No

Don't know/Not sure

Refuse to answer

5. Are you Hispanic or Latino?

Yes

No

Don't know/Not sure

Refuse to answer

6. What is your race? Please select all that apply.

White or Caucasian

Black or African American

Asian

Native Hawaiian or Other Pacific Islander

American Indian or Alaska Native

Other, please specify: _____ *

Don't know/Not sure

Refuse to answer

7. What is the highest grade or year of school you have completed?

Never attended school or only attended kindergarten
Grades 1-8
Grades 9-11
Regular high school diploma or GED
Trade school certificate/diploma
Some college credit, but less than one year of college credit
One or more years of college credit, no degree
Associate degree
Bachelor's degree
Master's degree
Professional degree beyond a Bachelor's degree
Professional degree beyond a Master's degree
Doctoral degree

8. What is your annual household income from all sources?

Less than \$15,000
\$15,000 to \$24,999
\$25,000 to \$39,999
\$40,000 to \$59,999
\$60,000 to \$74,999
\$75,000 to \$99,999
\$100,000 to \$149,999
\$150,000 to \$199,999
\$200,000 or more
Don't know/Not sure
Refuse to answer

9. What is the county where you currently live?

Barnstable
Berkshire
Bristol
Dukes
Essex
Franklin
Hampden
Hampshire
Middlesex
Nantucket
Norfolk
Plymouth
Suffolk
Worcester
Don't know/Not sure
Refuse to answer

10. Do you currently identify as having an ambulatory disability that limits your ability to be mobile?*

- Yes, I have an ambulatory disability
- No, I do not have an ambulatory disability
- Don't know/Not sure
- Refuse to answer

Marijuana and Marijuana Product Use

11. During the past 30 days, on how many days did you use marijuana or marijuana products?

- Number of days (1-30): _____ *
- None (0 days) – Skip to Q53
- Don't know/Not sure
- Refuse to answer

12. During the past 30 days, which of the following purpose(s) did you use marijuana or marijuana products for and on how many days? *Please select all that apply.*

- Recreational use (Non-medical, e.g., to get high). Number of days (1-30): _____
- Medical use certified by a qualified practitioner. Number of days (1-30): _____
- Medical use NOT certified by a qualified practitioner. Number of days (1-30): _____
- Don't know/Not sure
- Refuse to answer

If you do not use marijuana or marijuana products for medical use (certified or not certified), then skip to Q15.

If you are not taking this survey with a computer or tablet, then skip to Q14.

13. If you use marijuana for medical purposes, please indicate which medical condition(s) you use marijuana or marijuana products for. *Please select all that apply.*

- ADHD
- Alcohol Dependency
- Anxiety
- Arthritis
- Asthma
- Bipolar Disorder
- Bowel Distress
- Cancer
- Carpal Tunnel
- Chronic Pain
- Crohn's Disease
- Depression
- Diabetes
- Fibromyalgia

Glaucoma
Headaches/Migraines
Hepatitis C
HIV/AIDS
Huntington's Disease
Hypertension
Insomnia
Loss of Appetite
Multiple Sclerosis
Muscle Spasms
Muscular Dystrophy
Nausea
Neuropathy
OCD
Opioid Use
Osteoarthritis
PTSD
Schizophrenia
Seizures
Skin Conditions
Sleep Apnea
Stress
Tourette's Syndrome
Tremors
Vomiting
Wasting
Weight Loss
Other, please specify: _____ *
Don't know/Not sure
Refuse to answer

If you are not taking this survey with a smartphone, then skip to Q15.

14. If you use marijuana for medical purposes, please indicate which medical condition(s) you use marijuana or marijuana products for. *Please select all that apply.*

ADHD
Alcohol Dependency
Anxiety
Arthritis
Asthma
Bipolar Disorder
Bowel Distress
Cancer
Carpal Tunnel
Chronic Pain
Crohn's Disease

Depression
Diabetes
Fibromyalgia
Glaucoma
Headaches/Migraines
Hepatitis C
HIV/AIDS
Huntington's Disease
Hypertension
Insomnia
Loss of Appetite
Multiple Sclerosis
Muscle Spasms
Muscular Dystrophy
Nausea
Neuropathy
OCD
Opioid Use
Osteoarthritis
PTSD
Schizophrenia
Seizures
Skin Conditions
Sleep Apnea
Stress
Tourette's Syndrome
Tremors
Vomiting
Wasting
Weight Loss
Other, please specify: _____ *
Don't know/Not sure
Refuse to answer

15. Do you typically use marijuana or marijuana products that are higher in THC (delta-9-tetrahydrocannabinol), higher in CBD (cannabidiol), or that contain somewhat equal amounts of THC and CBD?

Higher in THC
Higher in CBD
Contain somewhat equal amounts of THC and CBD
Don't know/Not sure
Refuse to answer

If you are not taking this survey with a computer or tablet, then skip to Q17.

16. What method(s) of marijuana administration have you used (one time or more) in the past 30 days? *Please select all that apply.*

Smoked dried flower



Vaporized dried flower



Vaporized concentrate (cartridge/vape oil)



Dabbed marijuana products (butane hash oil, wax, shatter, etc.)



Ate marijuana products (brownies, cakes, cookies, etc.)



Drank marijuana infused products (tea, cola, alcohol, etc.)



Used sublingual (under the tongue) or orally administered uptake products (dissolvable strips, sublingual sprays, oils, tinctures, medicated lozenges, etc.)



Used oral capsules/tablets



Applied topical cannabis oil, ointment, lotion, cream, salve, etc. to your skin



Used rectal/vaginal cannabis suppositories



Other



If you are not taking this survey with a smartphone, then skip to Q18.

17. What method(s) of marijuana administration have you used (one time or more) in the past 30 days? *Please select all that apply.*

Smoked dried flower



Vaporized dried flower



Vaporized concentrate (cartridge/vape oil)



Dabbed marijuana products (butane hash oil, wax, shatter, etc.)



Ate marijuana products (brownies, cakes, cookies, etc.)



Drank marijuana infused products (tea, cola, alcohol, etc.)



Used sublingual (under the tongue) or orally administered uptake products (dissolvable strips, sublingual sprays, oils, tinctures, medicated lozenges, etc.)



Used oral capsules/tablets



Applied topical cannabis oil, ointment, lotion, cream, salve, etc. to your skin



Used rectal/vaginal cannabis suppositories



Other



If you do not administer marijuana or marijuana products in and “Other” way, skip to Q19.

18. Please specify the "Other" form marijuana administration you have used (one time or more) in the past 30 days.

Marijuana and Marijuana Product Use

If you have not “Smoked dried flower” in the past 30 days, skip to Q22.

19. How frequently did you smoke dried flower in a joint, bong, pipe, blunt, etc. in the past 30 days?

Once in the past 30 days

2-3 times in the past 30 days

Once per week

2-3 times per week

4-6 times per week

Once per day

Several times per day

Don't know/Not sure

Refuse to answer

If you are not taking this survey with a computer or tablet, then skip to Q21.

20. How much dried flower did you smoke in the past 30 days? *Below is a visual guide for dried flower quantities.*



Less than 1 gram

1 to 3 grams

1/8 ounce (or about 3.5 grams)

1/4 ounce (or about 7.0 grams)

1/2 ounce (or about 14.2 grams)

3/4 ounce (or about 21.3 grams)

1 ounce (or about 28.4 grams)

More than 1 ounce (more than 28.4 grams), please specify: _____*

Don't know/Not sure

Refuse to answer

If you are not taking this survey with a smartphone, then skip to Q22.

21. How much dried flower did you smoke in the past 30 days? *Below is a visual guide for dried flower quantities.*



Less than 1 gram

1 to 3 grams

1/8 ounce (or about 3.5 grams)

- 1/4 ounce (or about 7.0 grams)
- 1/2 ounce (or about 14.2 grams)
- 3/4 ounce (or about 21.3 grams)
- 1 ounce (or about 28.4 grams)
- More than 1 ounce (more than 28.4 grams), please specify: _____*
- Don't know/Not sure
- Refuse to answer

Marijuana and Marijuana Product Use

If you have not “Vaporized dried flower” in the past 30 days, skip to Q25.

22. How frequently did you vaporize dried flower in an e-cigarette-like vaporizer in the past 30 days?

- Once in the past 30 days
- 2-3 times in the past 30 days
- Once per week
- 2-3 times per week
- 4-6 times per week
- Once per day
- Several times per day
- Don't know/Not sure
- Refuse to answer

If you are not taking this survey with a computer or tablet, then skip to Q24.

23. How much dried flower did you vaporize in the past 30 days? *Below is a visual guide for dried flower quantities.*



- Less than 1 gram
- 1 to 3 grams
- 1/8 ounce (or about 3.5 grams)
- 1/4 ounce (or about 7.0 grams)
- 1/2 ounce (or about 14.2 grams)
- 3/4 ounce (or about 21.3 grams)
- 1 ounce (or about 28.4 grams)
- More than 1 ounce (more than 28.4 grams), please specify: _____*
- Don't know/Not sure
- Refuse to answer

If you are not taking this survey with a smartphone, then skip to Q25.

24. How much dried flower did you vaporize in the past 30 days? *Below is a visual guide for dried flower quantities.*



Less than 1 gram

1 to 3 grams

1/8 ounce (or about 3.5 grams)

1/4 ounce (or about 7.0 grams)

1/2 ounce (or about 14.2 grams)

3/4 ounce (or about 21.3 grams)

1 ounce (or about 28.4 grams)

More than 1 ounce (more than 28.4 grams), please specify: _____*

Don't know/Not sure

Refuse to answer

Marijuana and Marijuana Product Use

If you have not “Vaporized marijuana concentrate” in the past 30 days, skip to Q28.

25. How frequently did you vaporize marijuana concentrate (cartridge/vape oil) in an e-cigarette-like or other vaporizer in the past 30 days?

Once in the past 30 days

2-3 times in the past 30 days

Once per week

2-3 times per week

4-6 times per week

Once per day

Several times per day

Don't know/Not sure

Refuse to answer

26. How much THC did you administer in total in the past 30 days by vaporizing concentrate/vape oil?

None in the past 30 days

Less than 10 mg THC

10 to 30 mg THC

30 to 70 mg THC

70 to 100 mg THC

100 to 150 mg THC

150 to 200 mg THC

200 to 300 mg THC

More than 300 mg THC, please specify: _____ *

Don't know/Not sure

Refuse to answer

27. How much CBD did you administer in total in the past 30 days by vaporizing concentrate/vape oil?

None in the past 30 days

Less than 10 mg CBD

10 to 30 mg CBD

30 to 70 mg CBD

70 to 100 mg CBD

100 to 150 mg CBD

150 to 200 mg CBD

200 to 300 mg CBD

More than 300 mg CBD, please specify: _____ *

Don't know/Not sure

Refuse to answer

Marijuana and Marijuana Product Use

If you have not "Dabbed marijuana products" in the past 30 days, skip to Q31.

28. How frequently did you dab marijuana products (butane hash oil, wax, shatter, or other concentrates) in the past 30 days?

Once in the past 30 days

2-3 times in the past 30 days

Once per week

2-3 times per week

4-6 times per week

Once per day

Several times per day

Don't know/Not sure

Refuse to answer

29. How much THC did you administer in total in the past 30 days by dabbing butane hash oil, wax, shatter, or other concentrates?

None in the past 30 days

Less than 10 mg THC

10 to 30 mg THC

30 to 70 mg THC

70 to 100 mg THC

100 to 150 mg THC

150 to 200 mg THC

200 to 300 mg THC

More than 300 mg THC, please specify: _____ *

Don't know/Not sure

Refuse to answer

30. How much CBD did you administer in total in the past 30 days by dabbing butane hash oil, wax, shatter, or other concentrates?

None in the past 30 days

Less than 10 mg CBD

10 to 30 mg CBD

30 to 70 mg CBD

70 to 100 mg CBD

100 to 150 mg CBD

150 to 200 mg CBD

200 to 300 mg CBD

More than 300 mg CBD, please specify: _____ *

Don't know/Not sure

Refuse to answer

Marijuana and Marijuana Product Use

If you have not "Ate marijuana or marijuana products" in the past 30 days, skip to Q34.

31. How frequently did you eat marijuana or marijuana products in brownies, cakes, cookies, candy, etc. in the past 30 days?

Once in the past 30 days

2-3 times in the past 30 days

Once per week

2-3 times per week

4-6 times per week

Once per day

Several times per day

Don't know/Not sure

Refuse to answer

32. How much THC did you administer in total in the past 30 days by eating marijuana products (brownies, cakes, cookies, candy, etc.)?

None in the past 30 days

Less than 10 mg THC

10 to 30 mg THC

30 to 70 mg THC

70 to 100 mg THC

100 to 150 mg THC

150 to 200 mg THC

200 to 300 mg THC

More than 300 mg THC, please specify: _____ *

Don't know/Not sure

Refuse to answer

33. How much CBD did you administer in total in the past 30 days by eating marijuana products (brownies, cakes, cookies, candy, etc.)?

None in the past 30 days

Less than 10 mg CBD

10 to 30 mg CBD

30 to 70 mg CBD

70 to 100 mg CBD

100 to 150 mg CBD

150 to 200 mg CBD

200 to 300 mg CBD

More than 300 mg CBD, please specify: _____ *

Don't know/Not sure

Refuse to answer

Marijuana and Marijuana Product Use

If you have not “Drank marijuana infused products” in the past 30 days, skip to Q37.

34. How frequently did you drink marijuana infused products in tea, cola, alcohol, etc. in the past 30 days?

Once in the past 30 days

2-3 times in the past 30 days

Once per week

2-3 times per week

4-6 times per week

Once per day

Several times per day

Don't know/Not sure

Refuse to answer

35. How much THC did you administer in total in the past 30 days by drinking marijuana infused products (tea, cola, alcohol, etc.)?

None in the past 30 days

Less than 10 mg THC

10 to 30 mg THC

30 to 70 mg THC

70 to 100 mg THC

100 to 150 mg THC

150 to 200 mg THC

200 to 300 mg THC

More than 300 mg THC, please specify: _____ *

Don't know/Not sure

Refuse to answer

36. How much CBD did you administer in total in the past 30 days by drinking marijuana infused products (tea, cola, alcohol, etc.)?

None in the past 30 days

Less than 10 mg CBD

10 to 30 mg CBD

30 to 70 mg CBD

70 to 100 mg CBD

100 to 150 mg CBD

150 to 200 mg CBD

200 to 300 mg CBD

More than 300 mg CBD, please specify: _____ *

Don't know/Not sure

Refuse to answer

Marijuana and Marijuana Product Use

If you have not “Used sublingual (under-the-tongue) or orally administered uptake products” in the past 30 days, skip to Q40.

37. How frequently did you use sublingual (under-the-tongue) or orally administered uptake products (dissolvable strips, sublingual sprays, oils, tinctures, medicated lozenges, etc.) in the past 30 days?

Once in the past 30 days

2-3 times in the past 30 days

Once per week

2-3 times per week

4-6 times per week

Once per day

Several times per day

Don't know/Not sure

Refuse to answer

38. How much THC did you administer in total in the past 30 days by using sublingual (under-the-tongue) or orally administered uptake products (dissolvable strips, sublingual sprays, tinctures, medicated lozenges, etc.)?

None in the past 30 days

Less than 10 mg THC

10 to 30 mg THC

30 to 70 mg THC

70 to 100 mg THC

100 to 150 mg THC

150 to 200 mg THC

200 to 300 mg THC

More than 300 mg THC, please specify: _____*

Don't know/Not sure

Refuse to answer

39. How much CBD did you administer in total in the past 30 days by using sublingual (under-the-tongue) or orally administered uptake products (dissolvable strips, sublingual sprays, tinctures, medicated lozenges, etc.)?

None in the past 30 days

Less than 10 mg CBD

10 to 30 mg CBD

30 to 70 mg CBD

70 to 100 mg CBD

100 to 150 mg CBD

150 to 200 mg CBD

200 to 300 mg CBD

More than 300 mg CBD, please specify: _____*

Don't know/Not sure

Refuse to answer

Marijuana and Marijuana Product Use

If you have not "Used oral capsules/tablets" in the past 30 days, skip to Q43.

40. How frequently did you use oral capsules/tablets (THC and/or CBD pills) in the past 30 days?

Once in the past 30 days

2-3 times in the past 30 days

Once per week

2-3 times per week

4-6 times per week

Once per day

Several times per day

Don't know/Not sure

Refuse to answer

41. How much THC did you administer in total in the past 30 days by using oral capsules/tablets?

None in the past 30 days

Less than 10 mg THC

10 to 30 mg THC

30 to 70 mg THC

70 to 100 mg THC

100 to 150 mg THC

150 to 200 mg THC

200 to 300 mg THC

More than 300 mg THC, please specify: _____ *

Don't know/Not sure

Refuse to answer

42. How much CBD did you administer in total in the past 30 days by using oral capsules/tablets?

None in the past 30 days

Less than 10 mg CBD

10 to 30 mg CBD

30 to 70 mg CBD

70 to 100 mg CBD

100 to 150 mg CBD

150 to 200 mg CBD

200 to 300 mg CBD

More than 300 mg CBD, please specify: _____ *

Don't know/Not sure

Refuse to answer

Marijuana and Marijuana Product Use

If you have not “Applied topical cannabis oil, ointment, lotion, salve, etc.” in the past 30 days, skip to Q46.

43. How frequently did you apply topical cannabis oil, ointment, lotion, salve, etc. to your skin in the past 30 days?

Once in the past 30 days

2-3 times in the past 30 days

Once per week

2-3 times per week

4-6 times per week

Once per day

Several times per day

Don't know/Not sure

Refuse to answer

44. How much THC did you administer in total in the past 30 days by applying topical cannabis oil, ointment, lotion, salve, etc. to your skin?

None in the past 30 days

Less than 10 mg THC

10 to 30 mg THC

30 to 70 mg THC

70 to 100 mg THC

100 to 150 mg THC

150 to 200 mg THC

200 to 300 mg THC

More than 300 mg THC, please specify: _____ *

Don't know/Not sure

Refuse to answer

45. How much CBD did you administer in total in the past 30 days by applying topical cannabis oil, ointment, lotion, salve, etc. to your skin?

None in the past 30 days

Less than 10 mg CBD

10 to 30 mg CBD

30 to 70 mg CBD

70 to 100 mg CBD

100 to 150 mg CBD

150 to 200 mg CBD

200 to 300 mg CBD

More than 300 mg CBD, please specify: _____ *

Don't know/Not sure

Refuse to answer

Marijuana and Marijuana Product Use

If you have not "Used rectal/vaginal cannabis suppositories" in the past 30 days, skip to Q49.

46. How frequently did you use rectal/vaginal cannabis suppositories in the past 30 days?

Once in the past 30 days

2-3 times in the past 30 days

Once per week

2-3 times per week

4-6 times per week

Once per day

Several times per day

Don't know/Not sure

Refuse to answer

47. How much THC did you administer in total in the past 30 days by using rectal/vaginal cannabis suppositories?

None in the past 30 days

Less than 10 mg THC

10 to 30 mg THC

30 to 70 mg THC

70 to 100 mg THC

100 to 150 mg THC

150 to 200 mg THC

200 to 300 mg THC

More than 300 mg THC, please specify: _____ *

Don't know/Not sure

Refuse to answer

48. How much CBD did you administer in total in the past 30 days by using rectal/vaginal cannabis suppositories?

None in the past 30 days

Less than 10 mg CBD

10 to 30 mg CBD

30 to 70 mg CBD

70 to 100 mg CBD

100 to 150 mg CBD

150 to 200 mg CBD

200 to 300 mg CBD

More than 300 mg CBD, please specify: _____ *

Don't know/Not sure

Refuse to answer

Marijuana and Marijuana Product Use

If you have not "Use marijuana or marijuana products in some other way" in the past 30 days, skip to Q52.

49. How many times did you use marijuana or marijuana products in some other way (Q18 value) in the past 30 days?

Once in the past 30 days

2-3 times in the past 30 days

Once per week

2-3 times per week

4-6 times per week

Once per day

Several times per day

Don't know/Not sure

Refuse to answer

50. How much THC did you administer in total in the past 30 days by some other way (Q18 value)?

None in the past 30 days

Less than 10 mg THC

10 to 30 mg THC

30 to 70 mg THC

70 to 100 mg THC

100 to 150 mg THC

150 to 200 mg THC

200 to 300 mg THC

More than 300 mg THC, please specify: _____ *

Don't know/Not sure

Refuse to answer

51. How much CBD did you administer in total in the past 30 days by some other way (Q18 value)?

None in the past 30 days

Less than 10 mg CBD

10 to 30 mg CBD

30 to 70 mg CBD

70 to 100 mg CBD

100 to 150 mg CBD

150 to 200 mg CBD

200 to 300 mg CBD

More than 300 mg CBD, please specify: _____ *

Don't know/Not sure

Refuse to answer

Marijuana and Marijuana Product Use

52. During the past 30 days, about how much money did you spend on marijuana or marijuana products in total? Please enter zero if you spent no money on marijuana or marijuana products.

\$: _____ *

Don't know/Not sure

Refuse to answer

Perceptions of Medical Use of Marijuana

53. How long have you been using marijuana or marijuana products for medical purposes?

0 – 3 months

3 – 6 months

6 – 12 months

1 – 3 years

Greater than 3 years, please specify: _____ *

54. When you buy medical marijuana at a licensed dispensary, how do you feel about your personal safety?

- Very unsafe
- Somewhat unsafe
- Somewhat safe
- Very safe
- Don't know/Not sure
- Refuse to answer

55. When selecting a marijuana product for your medical use, how would you rate your current knowledge of the recommended product based on information provided by your certified practitioner?

- Very low
- Somewhat low
- Average
- Somewhat high
- Very high
- Don't know/Not sure
- Refuse to answer

56. When purchasing marijuana or marijuana products at a licensed dispensary, how confident do you feel that you are receiving a safe, uncontaminated product?

- Very low confidence
- Low confidence
- Average confidence
- Somewhat high confidence
- Very high confidence
- Don't know/Not sure
- Refuse to answer

57. How effective do you feel marijuana or marijuana products have been in treating the medical condition for which you are using it?

- Not effective at all
- A little effective
- Somewhat effective
- Effective
- Very Effective
- Don't know/Not sure
- Refuse to answer

Driving and Other Issues Related to Marijuana Use

58. Do you operate a motor vehicle at least once a week?*

Yes

No

Don't know/Not sure

Refuse to answer

59. During the past 30 days, how many times did you drive/operate a car or other motor vehicle when you were under the influence of (impaired from) marijuana or marijuana products?

0 times

1 time

2-3 times

4-5 times

6 or more times

Don't know/Not sure

Refuse to answer

60. During the past 30 days, how many times did you ride as a passenger in a car or other motor vehicle when the driver was under the influence of (impaired from) marijuana or marijuana products?

0 times

1 time

2-3 times

4-5 times

6 or more times

Don't know/Not sure

Refuse to answer

61. During the past 30 days, how many times were you treated in an emergency room or urgent care facility for any reason related to marijuana or marijuana product use?

Number of times: _____*

No emergency/urgent care related to marijuana or marijuana product use in the past 30 days

Don't know/Not sure

Refuse to answer

If you have used marijuana or marijuana products for less than 6 months, skip to Q65.

62. In the past 12 months, have you needed to consume larger amounts of marijuana or marijuana products in order to feel the same effects?

Yes

No

Don't know/Not sure

Not applicable (has used marijuana less than 12 months)

Refuse to answer

63. In the past 12 months, have you tried to cut down on your marijuana or marijuana product use?

Yes

No – Skip to Q65

Don't know/Not sure – Skip to Q65

Not applicable (has used marijuana less than 12 months) – Skip to Q65

Refuse to answer – Skip to Q65

64. In the past 12 months, have you felt sick or had withdrawal symptoms because you stopped or cut down on your marijuana or marijuana product use?

Yes

No

Don't know/Not sure

Not applicable (has used marijuana less than 12 months)

Refuse to answer

65. Have you noticed any of the following *negative outcomes/consequences related to your marijuana use? Please select all that apply.*

Negative changes in mood or mental health (worse depression, anxiety, etc.)

Reduction in physical health (you feel worse, can do fewer things, etc.)

Negative changes in cognition (difficultly thinking, remembering things, etc.)

Negative changes in social relationships

Occupation/job-related issues

Other, please specify: _____*

No negative outcomes/consequences

Don't know/Not sure

Refuse to answer

66. Have you noticed any of the following *positive outcomes/consequences* related to your marijuana use? *Please select all that apply.*

Positive changes in mood or mental health (depression or anxiety is better, etc.)

Improved physical health (you feel better, can do more, etc.)

Positive changes in cognition (easier time thinking, better at remembering things, etc.)

Positive changes in social relationships

Other, please specify: _____*

No positive outcomes/consequences

Don't know/Not sure

Refuse to answer

Alcohol Consumption

67. During the past 30 days, how many days did you have at least one drink of any alcoholic beverage such as beer, wine, a malt beverage or liquor? *One drink is equivalent to a 12-ounce beer, a 5-ounce glass of wine, or a drink with one shot of liquor.*

Number of days (1-30): _____*

No drinks of alcohol in the past 30 days

Don't know/Not sure

Refuse to answer

68. During the past 30 days, about how much money did you spend on alcohol in total? Please enter zero if you spent no money on alcohol. *We define expenditures on alcohol as the total amount spent on the alcohol consumed in the past 30 days and not alcohol purchased for other purposes like gifts or storage.*

\$: _____*

Don't know/Not sure

Refuse to answer

If you have not had at least one drink of any alcoholic beverage in the past 30 days, skip to Q70.

69. During the past 30 days, how many times did you drive/operate a car or other motor vehicle while you were under the influence of alcohol? *We define vehicle as a motorized vehicle, like a car, truck, SUV, or motorcycle driven on a public roadway.*

0 times

1 time

2-3 times

4-5 times

6 or more times

Don't know/Not sure

Refuse to answer

70. During the past 30 days, how many times did you ride as a passenger in a car or other motor vehicle when the driver was under the influence of alcohol?

- 0 times
- 1 time
- 2-3 times
- 4-5 times
- 6 or more times
- Don't know/Not sure
- Refuse to answer

71. During the past 30 days, how many times were you treated in an emergency room or urgent care facility for any reason related to alcohol use?

- Number of times: _____*
- No emergency/urgent care related to alcohol use in the past 30 days
- Don't know/Not sure
- Refuse to answer

Non-Medical Use of Prescription Drugs and Other Substances

72. During the past 30 days, did you use any of the following drugs for non-medical purposes (e.g., to get “high”)? *Please select all that apply.*

- Cocaine or Crack
- Heroin
- Antianxiety drugs such as (Sedatives/Tranquilizers/Anxiolytics)
- Sleeping drugs such as (Benzodiazepines, Barbiturates)
- Prescription opioids such as Oxycodone/OxyContin, Hydrocodone/Vicodin, Morphine, Methadone, Fentanyl
- Other, please specify: _____*
- None of these – Skip to Q74
- Don't know/Not sure – Skip to Q74
- Refuse to answer – Skip to Q74

73. During the past 30 days, on how many days did you use any of the drug(s) listed as answer choices above?

- Number of days (1-30): _____*
- Don't know/Not sure
- Refuse to answer

74. Since beginning to use marijuana, have you cut down or stopped using any other prescription drugs, over the counter medications, or other substances?

- Yes, please specify the substance(s) that were reduced or stopped: _____*
- No
- Don't know/Not sure
- Refuse to answer

75. During the past 30 days, about how much money did you spend on drugs, either prescription drugs or other substances, in total? Please enter zero if you spent no money on other drugs. *We define expenditures on other drugs as the total amount spent on the drug(s) listed above that were consumed in the past 30 days and non prescription drugs or other drugs purchased for other purposes like gifts or storage.*

\$: _____ *

Don't know/Not sure

Refuse to answer

If you have not used drugs in Q72 for non-medical purposes, skip to Q77.

76. During the past 30 days, how many times did you drive/operate a car or other motor vehicle when you were under the influence of any of the drug(s) indicated above?

0 times

1 time

2-3 times

4-5 times

6 or more times

Don't know/Not sure

Refuse to answer

77. During the past 30 days, how many times did you ride as a passenger in a car or other motor vehicle when the driver was under the influence of any of the drug(s) indicated above?

0 times

1 time

2-3 times

4-5 times

6 or more times

Don't know/Not sure

Refuse to answer

If you have not used drugs in Q72 for non-medical purposes, skip to Q79.

78. During the past 12 months, how many times were you treated in an emergency room or urgent care facility for any reason related to use of the drug(s) indicated above?

Number of times: _____ *

No emergency/urgent care treatment related to use of drugs indicated above in the past 12 months

Don't know/Not sure

Refuse to answer

Combination of Substances

79. During the past 30 days, on how many days did you use a combination of alcohol, marijuana, or other drugs, either prescription drugs or other substances?

- Number of days (1-30): _____ *
- None (0 days) – Skip to Q81
- Don't know/Not sure – Skip to Q81
- Refuse to answer – Skip to Q81

80. During the past 30 days, did you drive/operate a car or other vehicle when you were under the influence of (impaired from) any combination of alcohol, marijuana, or other drugs? For each option that you selected 'Yes', please also indicate the number of days in the past 30 days that you drove/operated a car or other vehicle when you were under the influence of the specified substances.

- No
- Yes, alcohol and marijuana. Number of days (1-30): _____ *
- Yes, alcohol and other drugs. Number of days (1-30): _____ *
- Yes, marijuana and other drugs. Number of days (1-30): _____ *
- Yes, alcohol, marijuana, and other drugs. Number of days (1-30): _____ *
- Don't know/Not sure
- Refuse to answer

Health Study

If you have an ambulatory disability and do not operate a motor vehicle at least once a week, skip to Q82.

81. Would you be interested in learning more about participating in a health study assessing marijuana levels in the bodies of medical use of marijuana patients?

- Yes (*A member from our study team may contact you*)
- No

Random Prize Drawing

82. Would you like to be entered into a random prize drawing to win a gift card worth \$100, \$250, or \$500 for your participation in this survey?

- Yes (*We will notify you by email if you are a winner*)
- No

Thank You!

You have reached the end of this survey. Thank you for your participation! If you have any questions about this survey, please call [REDACTED]

Appendix C
Economic and Fiscal Model Inputs

Table C.1. Model Inputs and Data Sources

Input Metric	Estimate or Range	Data Source
Domain: Sales and Business Tax Revenue		
Marijuana Consumption by MA Residents		
Number of residents in MA		
Adolescent	970,444	2015 ACS
Adult	4,991,000	2015 ACS
Percentage of MA residents with current marijuana use		
Adolescent	8.7–24.0	2015 YHS, 2015 YRBSS, 2015–2016 NSDUH
Post-legalization percentage change	(5)–4.5	Anderson, Hansen, & Rees (2015); Choo et al. (2014); Hasin et al. (2015); Wen, Hockenberry, & Cummings (2015); Dills et al. (2017)
Percentage purchasing from RMDs	0–60	Friese, Grube, & Moore (2013), authors' assumption
Adult	8.6–12.1	2015 BRFS, 2015 NSDUH
Post-legalization percentage change	15.9–16.6	Hasin et al. (2017); Wen et al. (2015)
Percentage shift from illicit to legal market	50–80	Stakeholder interview
Number of use days in past month, among users		
Regular users (1-20 use days per month)	7.26	Task 1 survey
Heavy users (21+ use days per month)	29.16	Task 1 survey
Percentage change in marijuana use days	12–17	Wen, Hockenberry, & Cummings (2014)
Percentage of users		
Regular users (1–20 use days per month)	67.94	Task 1 survey
Heavy users (21+ use days per month)	32.06	Task 1 survey
Grams of marijuana consumed each day of use		
Regular users (1-20 use days per month)	0.17–0.67	MBHS Task 1 survey, Kilmer et al. (2013)
Heavy users (21+ use days per month)	0.32–1.6	MBHS Task 1 survey, Kilmer et al. (2013)
Number of medical marijuana users	53872	
Current price of marijuana	\$13.3–\$13.7	RMD, Price of Weed, Budzu, Dispensary Sheets
Post-legalization percentage change	(50)–0	Stakeholder interview, WA State LCB (n.d.)
Tax rate	6.25% sales 10.75% excise 0-3% local	
Marijuana Consumption by Tourists		
Percentage of tax revenue generated from tourists	7–12	Light et al. (2016); Cooper et al. (2016)
Business tax rate on gross revenue	0.08	MA DOR
Beer Consumption		
Tax revenue from beer	72,830,435	Russell et al. (2017), Wide Open Eats (2017)

Input Metric	Estimate or Range	Data Source
Post-legalization percentage change in sales	(9.21–0.59)	Anderson, Hansen, & Rees (2013)
Domain: Regulatory Oversight		
State Regulatory and Law Enforcement		
Costs	\$1,778,944	WSIPP, CCC
Revenue	\$2,185,407	WSIPP, CCC
Domain: Law Enforcement		
Misdemeanor Arrests		
Unit cost	\$1,188	Aos, Phipps, Barnoski, & Lieb (2001)
Number ^a	240	Stakeholder interview
Post-legalization percentage change	(50–80)	WSIPP, stakeholder interview
Misdemeanor Convictions		
Unit cost	\$522	Aos et al. (2001)
Number ^a	159	Stakeholder interview
Post-legalization percentage change	(50–80)	WSIPP, stakeholder interview
Incarcerations		
Average annual cost of incarceration	\$53,041	Aos et al. (2011)
Number ^a	40	Stakeholder interview
Post-legalization percentage change	(50–80)	WSIPP, stakeholder interview
Supervised Release (Parolees/Probationers)		
Average annual cost of parole	\$4,180	Aos et al. (2011)
Number ^a	122	Stakeholder interview
Post-legalization percentage change	(50–80)	WSIPP, stakeholder interview
Traffic Fatalities		
Cost of cannabis impaired training	\$655,000	Stakeholder interview
Legal cost per crash involving fatalities	\$115,989	Blincoe, Miller, Zaloshnja, & Lawrence (2015)
Number	306	2015 FARS
Post-legalization percentage change	(11.4–9.8)	Anderson, Hansen, & Rees (2013); Santaella-Tenorio et al. (2017)
Domain: Public Health		
Medicaid prescription drug spending	\$459,769,135	Bradford and Bradford (2017)
Post-legalization percentage change	(1.09–1.99)	Bradford and Bradford (2017)
Cannabis abuse or dependence		
Cost of treatment to the state	\$2,086	Stakeholder interview
Treatment admissions	2,840	2016 TEDS
Post-legalization percentage change	10–27.2	Chu (2015); Wen et al. (2015); Hasin et al. (2017); Darnell & Bitney (2017)
Opioid abuse or dependence		
Cost of treatment to the state	\$1,039– \$4,221	Stakeholder interview, Birnbaum et al. (2011), 2011 TEDS
Treatment admissions	3,956	2016 TEDS
Post-legalization percentage change	(45.81)–22.47	Powell et al. (2015)
Averted Mortality		
Opioid-related mortality		
Number of overdose deaths	1,990	MPDH
Post-legalization percentage change	(18.00)– (17.90)	Powell et al. (2015); Bachhuber, Saloner, Cunningham, & Barry (2014)
Average income	\$60,840	2015 ACS

Input Metric	Estimate or Range	Data Source
Suicides		
Cost of a suicide to the state	\$39,887	Shepard, Gurewich, Lwin, Reed, & Silverman (2015)
Number of suicides, males age 20–29	76	2015 CDC Vital Statistics
Post-legalization percentage change	(18.8)–(3.8)	Anderson, Rees, & Sabia (2014)
Average income, males age 20–29	\$24,228	2015 ACS
Number of suicides, males age 30–39	77	2015 CDC Vital Statistics
Post-legalization percentage change	(17.5)–(2.4)	Anderson, Rees, & Sabia (2014)
Average income, males age 30–39	\$56,913	2015 ACS
Traffic fatalities	<i>see Law Enforcement section above</i>	
Average income	<i>see Opioid-related mortality above</i>	
Worker Productivity		
Number of recreational dispensaries	123	MDPH estimate
Average salary for minimum wage full-time employees ^{a,b}	\$22,000	\$11/hr, 40 hrs/wk, 50 wks/yr
Income tax rate	0.05	MA DOR
Number of FTEs at minimum wage per dispensary previously unemployed or working in illicit market ^b	0-10	Authors' assumption
Hourly earnings, employed males age 20–29		
Population total	340,203	2015 ACS
Average hourly earnings	\$15.6	2015 ACS
Post-legalization absolute change	(\$4.85)–(\$0.42)	Sabia and Nguyen (2016)
Average hours worked per week	37.4	2015 ACS
Average weeks worked per year	51	2015 ACS
Full-time employment, females age 50+ ^b		
Population total	532,394	2015 ACS
Average earnings per year	\$49,175	2015 ACS
Percentage employed full time ^b	28.5	2015 ACS
Post-legalization percentage change	1.34–17.48	Nicholas and Maclean (2016)
Hours worked per week, employed males age 50+		
Population total	539,526	Census
Average hourly earnings	\$34.1	ACS
Average hours worked per week	41.7	ACS
Average weeks worked per year	50	ACS
Post-legalization percentage change	(0.98)–10.78	Nicholas and Maclean (2016)

Sources: Mathematica's synthesis of estimates from the literature, key stakeholder interviews, and primary and secondary data sources on the impact of legalized adult use of marijuana in Massachusetts.

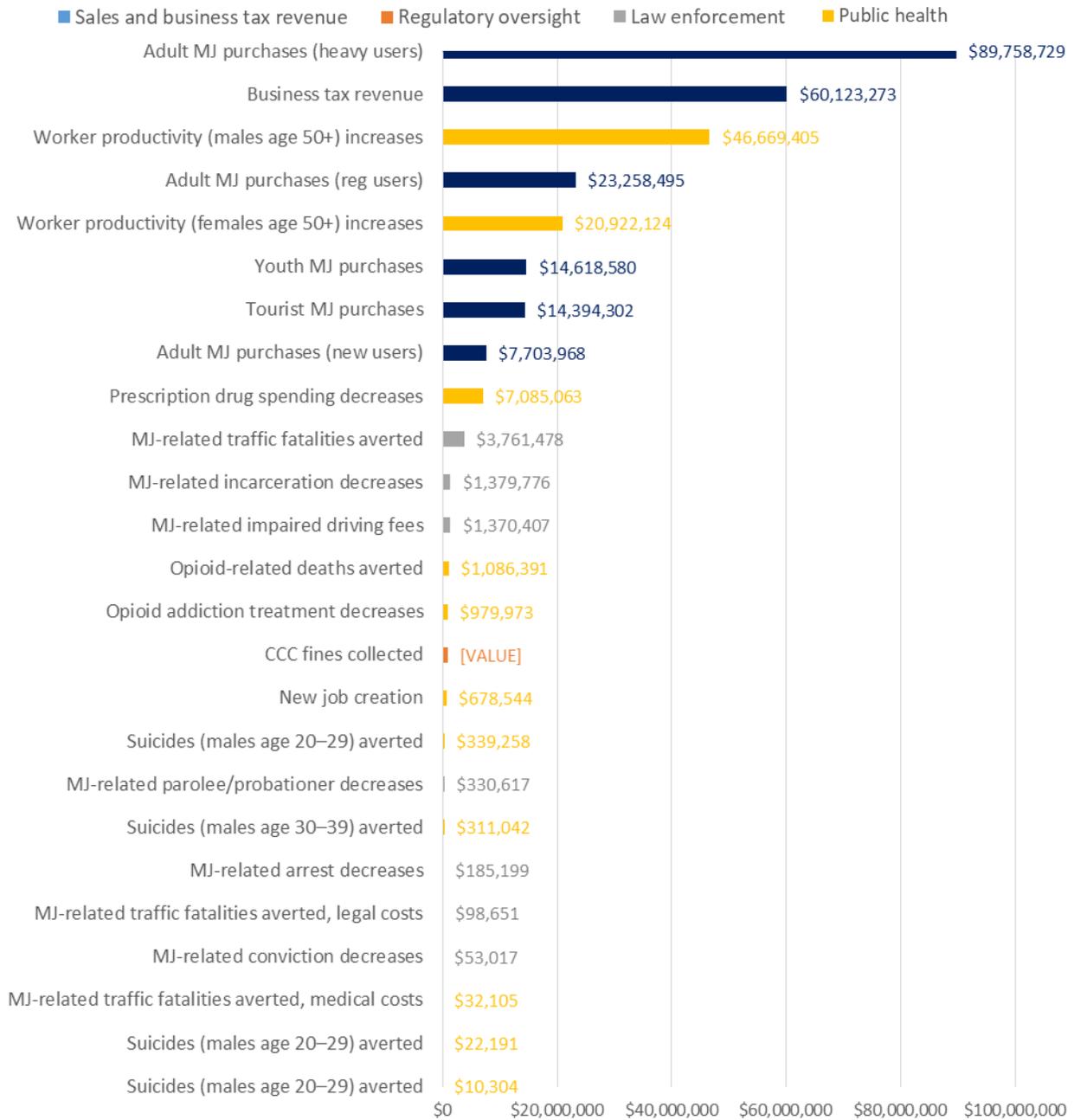
Note: Values in parentheses reflect negative values.

^a Values were calculated by the authors based on the data.

^b FTE = full-time employee, with full-time defined as working more than 35 hours per week.

ACS = American Community Survey; BRFSS = Behavioral Risk Factor Surveillance System; CCC = Cannabis Control Commission; CDC = Centers for Disease Control and Prevention; FARS = Fatality Analysis Reporting System; LCB = Liquor Cannabis Board; MA DOR = Massachusetts Department of Revenue.; MBHS = Marijuana Baseline Health Study; MDOC = Massachusetts Department of Corrections; MDPH = Massachusetts Department of Public Health; NSDUH = National Survey on Drug Use and Health; RMD = registered marijuana dispensary; TEDS = Treatment Episode Data Set; WSIPP = Washington State Institute for Public Policy; YHS = Massachusetts Youth Health Survey; YRBSS = Youth Risk Behavior Surveillance System.

Figure C.1. New Revenue or Savings Estimated Post-Legalization, by Source

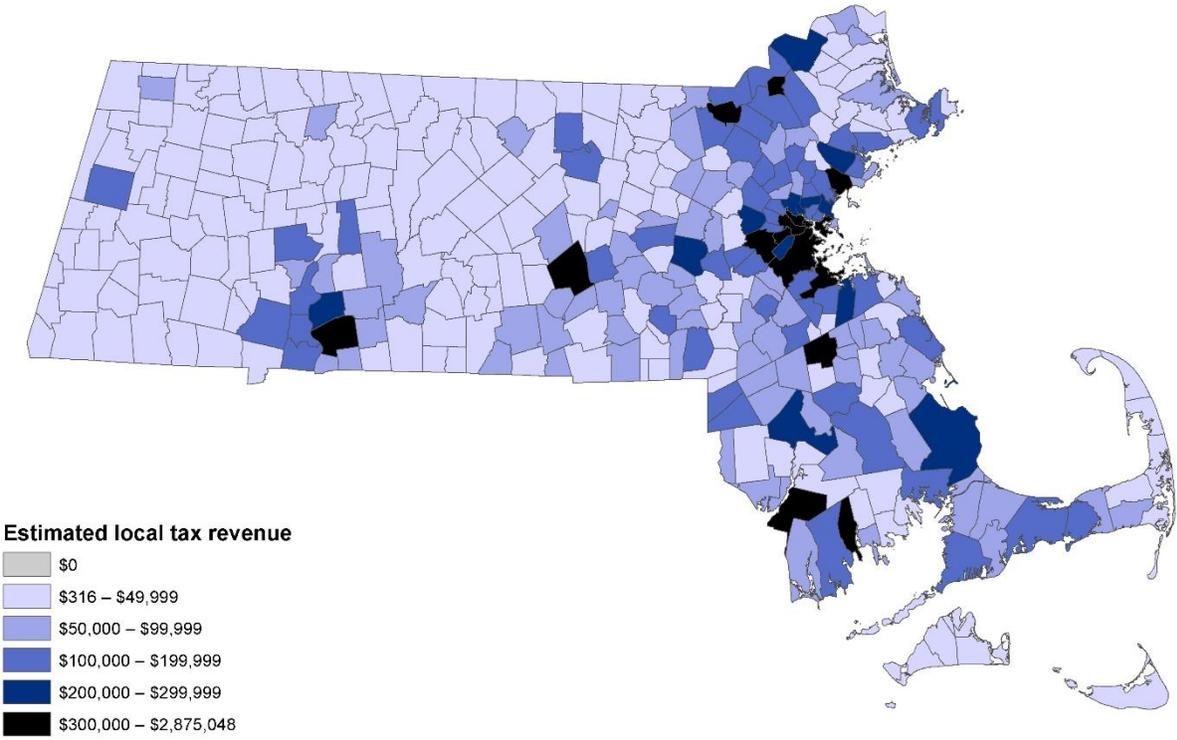


Sources: Mathematica’s analysis of impacts of legalized adult use of marijuana in Massachusetts using estimates from the literature, key stakeholder interviews, and primary and secondary data sources. See Appendix C Table C.1 for data sources used to inform these estimates.

Note: The table displays sources of revenue or savings and excludes measures associated with costs or losses.

CCC = Cannabis Control Commission; MJ = marijuana.

Figure C.2. Estimated Two-Year Local Tax Revenue if Registered Marijuana in all Cities/Towns



Sources: Mathematica’s analysis of impacts of legalized adult use of marijuana in Massachusetts using estimates from the literature, key stakeholder interviews, and primary and secondary data sources. See Appendix C Table C.1 for data sources used to inform these estimates.

Table C.2. Estimated Two-Year Local Tax Revenue if Registered Marijuana Dispensaries in all Cities/Towns

City or town type	Number of cities or towns	Estimated two-year local tax revenue		
		Median	Minimum	Maximum
Rural (< 100 people/km ²)	29	\$3,077	\$316	\$7,476
Suburban, low density (100–500 people/km ²)	60	\$7,713	\$1,926	\$32,340
Suburban, medium density (501–1,000 people/km ²)	64	\$29,375	\$9,242	\$110,963
Suburban, high density (1,001–10,000 people/km ²)	171	\$70,090	\$13,076	\$369,822
Urban (> 10,000 people/km ²)	27	\$258,946	\$56,766	\$2,875,048

Sources: Mathematica’s analysis of impacts of legalized adult use of marijuana in Massachusetts using estimates from the literature, key stakeholder interviews, and primary and secondary data sources. See Appendix C Table C.1 for data sources used to inform these estimate

Table C.3. Estimated Two Year Local Tax Revenue for each City or Town

City or town	Cities/towns with an RMD		With RMDs in all towns
	State-level # MJ users	Localized # MJ users	
Abington			\$75,951
Acton	\$507,245	\$501,976	\$95,128
Acushnet			\$43,548
Adams			\$34,745
Agawam			\$119,696
Alford			\$2,052
Amesbury			\$69,236
Amherst	\$239,344	\$236,474	\$157,773
Andover			\$138,626
Aquinnah			\$1,926
Arlington	\$650,422	\$643,467	\$186,356
Ashburnham			\$25,381
Ashby			\$13,531
Ashfield			\$6,773
Ashland			\$71,747
Athol			\$48,388
Attleboro	\$515,364	\$1,294,6	\$180,697
Auburn			\$68,323
Avon			\$17,602
Ayer	\$217,917	\$215,603	\$33,176
Barnstable			\$188,234
Barre	\$144,385	\$142,843	\$22,312
Becket			\$7,476
Bedford			\$58,009
Belchertown			\$55,595
Bellingham			\$65,061
Belmont			\$105,755
Berkley			\$26,713
Berlin			\$12,384

City or town	Cities/towns with an RMD		With RMDs in all towns
	State-level # MJ users	Localized # MJ users	
Bernardston			\$9,144
Beverly			\$167,852
Billerica			\$178,089
Blackstone			\$37,348
Blandford			\$4,851
Bolton			\$20,461
Boston	\$2,875,048	\$4,816,1	\$2,875,0
Bourne	\$83,143	\$82,148	\$83,143
Boxborough			\$21,507
Boxford			\$32,757
Boylston			\$18,378
Braintree			\$143,585
Brewster	\$192,128	\$189,911	\$41,897
Bridgewater	\$276,557	\$273,457	\$129,434
Brimfield			\$15,430
Brockton	\$435,068	\$894,904	\$435,068
Brookfield			\$14,032
Brookline	\$233,498	\$309,883	\$233,498
Buckland			\$7,682
Burlington	\$991,873	\$981,277	\$107,908
Cambridge	\$474,261	\$413,420	\$474,261
Canton	\$86,332	\$85,346	\$86,332
Carlisle			\$21,125
Carver			\$54,260
Charlemont			\$4,672
Charlton	\$64,597	\$63,862	\$54,530
Chatham			\$26,304
Chelmsford			\$147,046
Chelsea			\$159,798
Cheshire			\$13,357
Chester	\$64,590	\$63,872	\$6,337
Chesterfield			\$4,833
Chicopee	\$234,594	\$946,729	\$234,594
Chilmark			\$4,467
Clarksburg			\$6,722
Clinton			\$57,392
Cohasset			\$31,508
Colrain			\$7,098
Concord			\$80,965
Conway			\$7,406
Cummington			\$3,473
Dalton			\$28,105
Danvers	\$204,617	\$202,333	\$111,665
Dartmouth	\$146,365	\$82,655	\$146,365
Dedham			\$98,817
Deerfield	\$60,801	\$60,111	\$21,235
Dennis	\$170,113	\$168,123	\$60,694
Dighton			\$29,807
Douglas			\$34,794
Dover			\$21,918
Dracut			\$128,899
Dudley			\$47,651
Dunstable			\$13,839
Duxbury			\$70,371
East			\$66,230
East Brookfield			\$9,242
East			\$66,453
Eastham			\$21,389

City or town	Cities/towns with an RMD		With RMDs in all towns
	State-level # MJ users	Localized # MJ users	
Easthampton	\$94,629	\$93,525	\$62,383
Easton			\$97,376
Edgartown			\$18,002
Egremont			\$4,836
Erving			\$7,744
Essex			\$14,619
Everett			\$184,323
Fairhaven	\$95,521	\$94,415	\$67,594
Fall River	\$598,643	\$1,739,8	\$369,822
Falmouth			\$133,236
Fitchburg	\$272,497	\$551,828	\$166,944
Florida			\$3,009
Foxborough			\$67,167
Framingham	\$615,046	\$288,353	\$298,149
Franklin			\$124,936
Freetown			\$37,255
Gardner	\$216,371	\$702,916	\$84,381
Georgetown	\$285,596	\$282,577	\$33,794
Gill			\$7,043
Gloucester	\$177,177	\$175,121	\$121,745
Goshen			\$4,323
Gosnold			\$316
Grafton	\$310,085	\$306,819	\$74,769
Granby			\$24,029
Granville			\$6,864
Great Barrington	\$68,715	\$67,927	\$29,321
Greenfield	\$177,839	\$721,885	\$73,490
Groton			\$46,187
Groveland			\$27,167
Hadley	\$34,651	\$34,244	\$20,715
Halifax			\$35,887
Hamilton			\$32,159
Hampden			\$21,724
Hancock			\$3,007
Hanover	\$209,486	\$207,262	\$65,179
Hanson			\$48,330
Hardwick			\$12,557
Harvard			\$27,064
Harwich			\$51,760
Hatfield			\$12,805
Haverhill			\$251,613
Hawley			\$1,725
Heath			\$3,077
Hingham			\$104,370
Hinsdale			\$8,710
Holbrook	\$299,598	\$296,311	\$43,544
Holden			\$74,199
Holland	\$130,809	\$129,393	\$10,561
Holliston			\$58,686
Holyoke	\$373,639	\$914,954	\$165,223
Hopedale			\$24,159
Hopkinton			\$64,937
Hubbardston			\$18,321
Hudson	\$396,608	\$392,319	\$83,066
Hull			\$50,121
Huntington			\$7,611
Ipswich	\$106,752	\$105,582	\$55,660
Kingston			\$60,486

City or town	Cities/towns with an RMD		With RMDs in all towns
	State-level # MJ users	Localized # MJ users	
Lakeville	\$97,641	\$96,567	\$51,709
Lancaster			\$33,581
Lanesborough			\$12,459
Lawrence			\$313,394
Lee	\$61,948	\$61,236	\$24,864
Leicester	\$225,355	\$222,905	\$47,090
Lenox			\$21,109
Leominster	\$243,144	\$874,472	\$171,261
Leverett			\$8,329
Lexington			\$135,482
Leyden			\$2,795
Lincoln			\$29,611
Littleton			\$39,448
Longmeadow			\$65,150
Lowell	\$1,690,694	\$2,589,0	\$460,559
Ludlow			\$89,500
Lunenburg			\$45,485
Lynn	\$498,856	\$765,457	\$366,830
Lynnfield			\$49,910
Malden			\$258,946
Manchester			\$21,401
Mansfield	\$368,564	\$364,656	\$94,800
Marblehead			\$81,562
Marion			\$23,151
Marlborough			\$166,880
Marshfield			\$118,373
Mashpee	\$501,747	\$496,207	\$59,104
Mattapoisett			\$28,943
Maynard			\$44,254
Medfield			\$46,519
Medford			\$247,455
Medway			\$50,216
Melrose			\$116,834
Mendon			\$24,127
Merrimac	\$514,520	\$509,036	\$26,845
Methuen			\$196,644
Middleborough	\$125,781	\$124,338	\$110,963
Middlefield			\$2,019
Middleton			\$38,676
Milford			\$116,405
Millbury	\$170,775	\$168,911	\$55,443
Millis	\$610,722	\$604,410	\$31,070
Millville			\$13,076
Milton			\$105,128
Monroe			\$439
Monson			\$36,335
Montague			\$35,069
Monterey			\$3,696
Montgomery			\$3,584
Mount			\$674
Nahant			\$14,387
Nantucket	\$43,840	\$43,331	\$43,840
Natick			\$145,432
Needham	\$245,512	\$242,867	\$113,827
New Ashford			\$1,205
New Bedford	\$440,200	\$1,264,4	\$392,760
New Braintree			\$4,663
New			\$6,268

City or town	Cities/towns with an RMD		With RMDs in all towns
	State-level # MJ users	Localized # MJ users	
New Salem			\$4,303
Newbury			\$28,121
Newburyport			\$72,762
Newton	\$552,130	\$1,514,9	\$369,158
Norfolk			\$45,393
North Adams			\$57,063
North Andover			\$118,211
North			\$117,358
North Brookfield			\$19,656
North Reading			\$64,871
Northampton	\$121,055	\$521,510	\$110,653
Northborough			\$60,900
Northbridge			\$66,673
Northfield			\$12,498
Norton			\$80,587
Norwell	\$311,404	\$308,178	\$48,972
Norwood	\$280,605	\$277,567	\$113,341
Oak bluffs			\$19,058
Oakham			\$7,495
Orange	\$125,056	\$123,691	\$32,109
Orleans			\$25,419
Otis			\$6,523
Oxford	\$222,788	\$220,409	\$56,386
Palmer			\$50,709
Paxton			\$20,286
Peabody			\$214,906
Pelham			\$5,031
Pembroke			\$83,915
Pepperell			\$49,634
Peru			\$3,684
Petersham			\$4,940
Phillipston			\$7,258
Pittsfield	\$416,675	\$551,255	\$183,360
Plainfield			\$2,295
Plainville			\$34,132
Plymouth	\$415,479	\$102,924	\$272,645
Plympton			\$13,602
Princeton			\$14,184
Provincetown	\$20,872	\$20,610	\$13,102
Quincy	\$531,229	\$1,243,9	\$371,084
Randolph	\$408,061	\$403,573	\$131,193
Raynham			\$55,836
Reading			\$105,602
Rehoboth			\$48,945
Revere	\$1,251,436	\$1,237,8	\$232,870
Richmond			\$6,400
Rochester			\$24,972
Rockland	\$354,642	\$350,843	\$83,074
Rockport			\$29,465
Rowe			\$1,929
Rowley			\$24,553
Royalston			\$5,515
Russell			\$6,384
Rutland			\$33,874
Salem	\$681,457	\$2,420,7	\$175,511
Salisbury			\$36,033
Sandisfield			\$3,622
Sandwich			\$84,908

City or town	Cities/towns with an RMD		With RMDs in all towns
	State-level # MJ users	Localized # MJ users	
Saugus			\$113,936
Savoy			\$3,298
Scituate			\$84,114
Seekonk			\$59,858
Sharon	\$68,139	\$67,399	\$68,139
Sheffield			\$13,600
Shelburne			\$8,381
Sherborn			\$17,433
Shirley			\$32,066
Shrewsbury	\$271,046	\$739,408	\$148,062
Shutesbury			\$7,122
Somerset			\$76,402
Somerville	\$613,668	\$3,028,7	\$344,381
South Hadley			\$69,147
Southampton			\$22,977
Southborough	\$193,086	\$191,101	\$40,083
Southbridge			\$69,340
Southwick			\$40,192
Spencer			\$49,337
Springfield	\$988,088	\$3,309,6	\$625,013
Sterling			\$32,321
Stockbridge			\$8,845
Stoneham			\$93,397
Stoughton			\$110,345
Stow			\$28,706
Sturbridge	\$170,209	\$168,378	\$38,519
Sudbury			\$74,940
Sunderland			\$15,841
Sutton			\$37,441
Swampscott			\$56,766
Swansea			\$67,818
Taunton	\$356,548	\$157,621	\$233,927
Templeton			\$33,831
Tewksbury			\$127,724
Tisbury			\$16,969
Tolland			\$2,443
Topsfield			\$25,570
Townsend			\$38,684
Truro			\$7,153
Tyngsborough			\$50,554
Tyringham			\$1,717
Upton			\$31,093
Uxbridge			\$56,406
Wakefield			\$111,036
Wales			\$7,841
Walpole			\$95,734
Waltham			\$272,375
Ware			\$37,627
Wareham	\$217,119	\$217,119	\$105,441
Warren			\$21,491
Warwick			\$3,127
Washington			\$2,399
Watertown	\$439,564	\$434,488	\$143,331
Wayland			\$55,640
Webster			\$70,090
Wellesley			\$109,880
Wellfleet			\$13,275
Wendell			\$3,687

City or town	Cities/towns with an RMD		With RMDs in all towns
	State-level # MJ users	Localized # MJ users	
Wenham			\$21,005
West Boylston			\$33,548
West			\$32,795
West Brookfield			\$15,904
West Newbury			\$17,567
West Springfield	\$118,615	\$431,662	\$118,615
West			\$5,069
West Tisbury	\$76,956	\$76,108	\$10,785
Westborough			\$76,302
Westfield	\$235,284	\$529,505	\$173,124
Westford			\$95,132
Westhampton			\$6,611
Westminster	\$46,208	\$45,692	\$30,727
Weston			\$48,419
Westport			\$65,801
Westwood			\$57,456
Weymouth			\$217,369
Whately			\$5,863
Whitman			\$68,542
Wilbraham			\$59,967
Williamsburg			\$9,558
Williamstown			\$32,340
Wilmington			\$96,881
Winchendon			\$43,469
Winchester			\$90,509
Windsor			\$3,785
Winthrop			\$78,563
Woburn			\$166,385
Worcester	\$762,069	\$1,298,0	\$762,069
Worthington			\$4,851
Wrentham			\$43,133
Yarmouth			\$100,574

Sources: Mathematica’s analysis of impacts of legalized adult use of marijuana in Massachusetts using estimates from the literature, key stakeholder interviews, and primary and secondary data sources. See Appendix C Table C.1 for data sources used to inform these estimates.
 MJ = marijuana; RMD = registered marijuana dispensary.

Appendix D

Marijuana Product and Price Characterization

Introduction

Medical marijuana products that are sold in Massachusetts are required to be evaluated according to established laboratory testing protocols (DPH, 2016). Briefly, these protocols describe evaluating dispensed products for contaminants and cannabinoid content, inclusive of evaluating finished (dried) plant material, cannabis resin, and cannabis concentrates. As some of these products (e.g., oils and resins) are tested and later incorporated into marijuana-infused products (MIPs) intended for use as edibles (e.g., capsules, brownies, candy, etc.), or various personal care products (e.g., tinctures, lotions, suppositories, etc.), a marijuana-containing product may undergo multiple rounds of product testing before it is dispensed.

Marijuana products of a similar variety are generally priced according to the cannabinoid content. In August 2017 Registered Marijuana Dispensaries in Massachusetts were asked to complete a voluntary survey of retail marijuana prices to inform the economic and fiscal analyses being conducted as part of the MBHS.

This appendix describes an overview of the cannabinoid content and price of medical marijuana products that were available through the DPH Medical Use of Marijuana Program. As these medical marijuana products were likely to be very similar in composition to the types of products available in adult-use marketplace, an earlier draft of the information provided in this Appendix was used to inform various analyses in the MBHS. As such, a summary of the cannabinoid content and price of retail medical marijuana products available in Massachusetts over the period of May 14, 2015 through December 31, 2018 is included here as Appendix D.

Cannabinoid Content Summary

Marijuana products that are dispensed for medical use in Massachusetts must bear a label that identifies the percentage (by dry weight) of Δ^9 -tetrahydrocannabinol (Δ^9 -THC), cannabidiol (CBD), tetrahydrocannabinolic acid (THCa), and cannabidiolic acid (CBDa). Of these cannabinoids, Δ^9 -THC is the primary psychoactive component and cannabidiol (CBD) is the primary non-psychoactive component of cannabis.

While regulating the sale and use of medical marijuana in Massachusetts, DPH has evaluated over 15,000 laboratory reports, describing over 14,500 medical marijuana products, from thirteen different medical marijuana facilities. These reports have been voluntarily submitted to DPH and describe the laboratory testing of flower products (44.6%), MIPs (27.0%), and concentrates, such as resin (3.7%), oils (19.5%), shatter (3.0%), or wax (2.2%). Of these laboratory reports, a total of 12,375 describe an evaluation of cannabinoid profile testing that describes levels of: Δ^9 -tetrahydrocannabinol (Δ^9 -THC), cannabidiol (CBD), tetrahydrocannabinolic acid (THCa), and/or cannabidiolic acid (CBDa).

The types of products tested for cannabinoids include flower products (37.2%), concentrates (29.4%), and MIPs (33.3%; see Figure 1). Table 1 describes the

cannabinoid testing results for flower, concentrates and MIPs. The cannabinoid Delta (Δ)9-THC was detected in 93.3% of flower products, 98.6% of concentrate, and 95.2% of MIPs. The cannabinoid THCa was detected in 99.6% of flower products, 67.2% of concentrates, and 17.0% of MIPs. The cannabinoid CBD was detected in 27.9% of flower products, 56.6% of concentrates, and 33.1% of MIPs. The cannabinoid CBDA was detected in 50.3% of flower products, 53.2% of concentrates, and 7.1% of MIPs.

The cannabinoid content of the available products is shown in Table 2. Of the 4,605 flower samples tested, THCa concentrations were most often between 14-28%. Approximately 5% of flower samples had THCa concentrations greater than 28%. CBDA was rarely detected in flower samples, and never at a concentration greater than 28%. The majority of flower samples (43.6%), had THCa levels between 14 and 21%. Of the 3642 concentrate samples tested, the majority (38.2%) had THC concentrations between 60 and 80%. Approximately, 15.4% of concentrate samples had THC concentrations greater than 80%, while only 0.6% had CBD concentrations greater than 80%.

Retail Price Summary

A summary of the price of retail marijuana products available at 11 of the 12 open and operating RMD locations in August of 2017 is shown in Table 4. Similar products across various RMDs were combined to provide an overview and summary (e.g., same product types) using the RMD retail price survey found in Figure 2. The product's dose of THC (in milligrams) was calculated for any product with a dose presented as a percentage, using the product net weight (i.e., dose percentage multiplied by product net weight).

Reference

Massachusetts Department of Public Health (DPH), 2016. Protocol for sampling and analysis of finished medical marijuana products and marijuana-infused products for Massachusetts registered medical marijuana dispensaries. Available: <https://www.mass.gov/service-details/medical-use-of-marijuana-program-product-testing>

Table 1. Cannabinoids Present in Retail Marijuana Products (Δ 9-THC, THCa, CBD, and CBDA)

Product Type	Products Tested n	Detected n (% tested)	Not Detected n (% tested)
Δ9-THC			
Flower	4605	4295 (93.3%)	310 (6.7%)
Concentrate	3644	3594 (98.6%)	50 (1.4%)
MIPs	4126	3928 (95.2%)	198 (4.8%)
THCa			
Flower	4605	4587 (99.6%)	18 (0.4%)
Concentrate	3644	2447 (67.2%)	1197 (32.8%)
MIPs	4126	700 (17.0%)	3426 (83.0%)
CBD			
Flower	4605	1287 (27.9%)	3318 (72.1%)
Concentrate	3644	2061 (56.6%)	1583 (43.4%)
MIPs	4126	1367 (33.1%)	2759 (66.9%)
CBDA			
Flower	4605	2316 (50.3%)	2289 (49.7%)
Concentrate	3644	1939 (53.2%)	1705 (46.8%)
MIPs	4126	291 (7.1%)	3835 (92.9%)

Table 2. Characterization of Cannabinoid Concentration (weight percent) Levels in Flower and Concentrate Samples

Flower	THCa < 3%	THCa 3 - 7%	THCa 7 - 14%	THCa 14 - 21%	THCa 21 - 28%	THCa > 28%	Total Samples
	n %	n %	n %	n %	n %	n %	
	117 2.50%	137 3.00%	403 8.80%	2010 43.6%	1701 36.9%	237 5.10%	4605
Flower	CBDa < 3%	CBDa 3 - 7%	CBDa 7 - 14%	CBDa 14 - 21%	CBDa 21 - 28%	CBDa > 28%	Total Samples
	n %	n %	n %	n %	n %	n %	
	4308 93.6%	38 0.80%	173 3.80%	63 1.40%	22 0.50%	1 0.00%	4605
Concentrate	THC < 5%	THC 5 - 20%	THC 20 - 40%	THC 40 - 60%	THC 60 - 80%	THC > 80%	Total Samples
	n %	n %	n %	n %	n %	n %	
	144 4.00%	209 5.70%	517 14.2%	821 22.5%	1390 38.2%	561 15.4%	3642
	<i>*Total THC = $[\Delta 9\text{-THC}] + 0.8772*[\text{THCa}]$</i>						
	CBD < 5%	CBD 5 - 20%	CBD 20 - 40%	CBD 40 - 60%	CBD 60 - 80%	CBD > 80%	Total Samples
	n %	n %	n %	n %	n %	n %	
3061 84%	279 7.70%	135 3.70%	89 2.40%	55 1.50%	23 0.60%	3642	
<i>**Total CBD = $[\text{CBD}] + 0.8772*[\text{CBDa}]$</i>							

Table 3. Cannabinoid Content in Retail Marijuana Products

Product Type	25th percentile (% weight)	Median (% weight)	75th percentile (% weight)	95th percentile (% weight)	Maximum (% weight)
Flower	0.2	0.3	0.7	1.9	24.1
Concentrate	3.1	20.5	63.0	87.1	96.9
MIPs	0.1	0.2	0.5	4.5	75.2
Flower	16.3	20.0	23.3	28.0	45.4
Concentrate	13.7	45.5	71.5	84.4	99.8
MIPs	0.0	0.0	0.1	0.9	62.8
Flower	0.1	0.2	0.3	0.6	3.4
Concentrate	0.5	1.0	4.7	49.0	99.0
MIPs	0.1	0.1	0.5	5.8	92.0
Flower	0.1	0.1	0.2	12.5	28.3
Concentrate	0.1	0.2	0.4	12.1	64.2
MIPs	0.0	0.0	0.1	0.6	3.3

Table 4: Summary of Retail Product Prices Provided in RMD Survey

	Product Group	Type	Description	Product Weight	THC Dose	Retail Price
Concentrates	Resin	Rosin	Concentrate for vaporization	0.5-1g	50-85%	\$25-\$45
	Resin	Keif	Cold pressed bar for vaporization	7g	38%	\$100
	Vape Oil	Cartridge	Concentrate oil for vaporization	0.9mL	200-1000mg	\$25 - \$100
	Wax	Wax	Concentrate for vaporization	1g	900mg	\$50
	Vape Oil	Cartridge	Concentrate oil for vaporization	0.25-0.5g	30-90%	\$60 - \$75
	Shatter	Shatter	Solid concentrate for vaporization	1g	85%	\$60
	Oil	Extract or distillate	Extract or distillate for infusion	1g	65-87%	\$65-\$80
Dried Flower	Pre-roll	Joint/cigar/cigarette	Intended for smoking	1g	15-35%	\$15-\$20
	Flower	Finished flower	Various strains	1g	15-35%	\$15
	Flower	Finished flower	Various strains	3.5g	15-35%	\$50
	Flower	Finished flower	Strain blend	28g	15-30%	\$250
	Flower	Finished flower	Various strains	28.4g	15-35%	\$250-\$350
Edible MIPs	Capsule	Capsule	Infused for ingestion	1-2g	10-25mg	\$2.50-\$5
	Lozenge	Flavored hard confection	Infused for ingestion	6.5g	10mg	\$4-\$5
	Chocolate	Chocolate bar/nugget	Infused for ingestion	9-68g	10mg	\$4-\$10
	Beverage	Lemonade	Infused for ingestion	--	20mg	\$10
	Baked Good	Cookie/muffin	Infused for ingestion	--	10-85mg	\$10-\$40
	Gummy	Flavored gummy confection	Infused for ingestion	5g	25-50mg	\$12-\$23
	Chocolate	Chocolate bar/nugget	Infused for ingestion	9-68g	100mg	\$25-\$30
	Lozenge	Flavored hard confection	Infused for ingestion	6.5g	100mg	\$25-\$35
	Gummy	Gummy confection	Infused for ingestion	50-100g	100-500mg	\$30-\$80
	Cooking oil	Grapeseed oil	Infused for ingestion	188g	840mg	\$100
Non-Edible MIPs	Suppository	suppository	Rectal/vaginal use	2g	10mg	\$4
	Topical	Lip Balm	Stick for lip application	--	10.15mg	\$5
	Suppository	suppository	Rectal/vaginal use	2g	25mg	\$7-\$12
	Topical	Salve	Cream for dermal application	28.4g	8-25%	\$30-\$45
	Topical	Lotion	Cannabis infused topical lotion	112.5g	350-375mg	\$30-\$60
	Topical	Transdermal patch	Skin application	--	125mg	\$40
	Tincture	Tincture	Infused for sublingual application	30mL	500mg	\$60-\$75

Figure 1. Cannabinoid Testing Results of Retail Marijuana Products for Δ 9-THC, THCa, CBD, CBDa through December 31, 2018

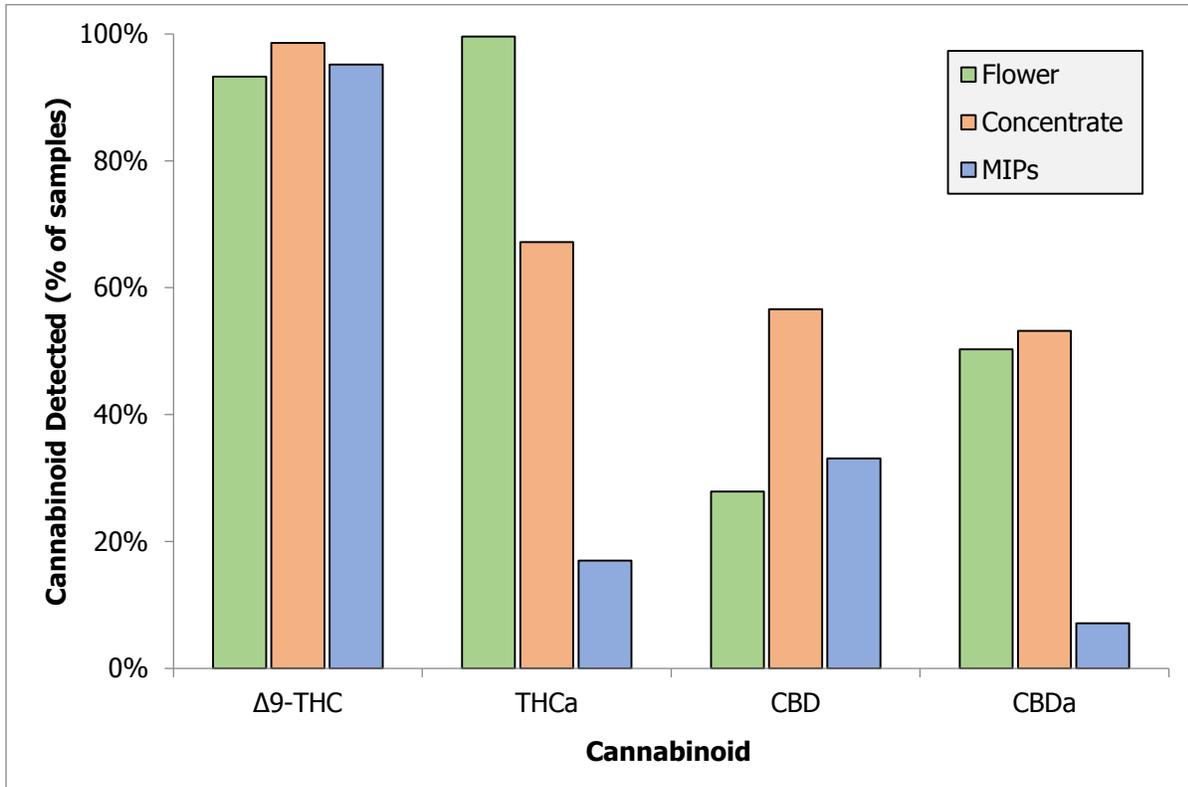


Figure 2: RMD Retail Price Survey*

RMD Name:

Category	Examples	Type	Description	Product Weight	Dose (Potency)	Retail Price
Dried Flower	Finished flower, pre-rolls, "Mini"-Pre-rolls					
Concentrates	Vape pen cartridge, oil, shatter, wax, resins, bubble hash, rosin					
Edible MIPs	Beverage, capsule, lozenge, gummy candy, brownie, cookie, honey, sauces/jams					
Non-Edible MIPs	Tincture, suppository, lotion/salve, massage oil, lip balm, patch, bath oils/salts					

****Instructions provided for filling out the above survey:***

Category: This column identifies the product-type category (i.e., dried flower, concentrate, edible MIPs, and non-edible MIPs).

Dried Flower: dried leaves and flowers of the female marijuana plant that have been trimmed and dried and include most importantly the inflorescences (i.e., “buds”) that may be used directly (e.g., smoked) as a medical product without further processing.

Concentrate: marijuana product derived by using solvents to extract and concentrate cannabinoid compounds (e.g., oils, pastes, waxes, or solids) or a solid medical marijuana product produced by gathering and compressing the cannabinoid-rich trichomes (i.e., keif) of the marijuana plant (e.g., cannabis resin, “hashish,” “hash,” or “bubble hash”).

Edible Marijuana-Infused Products (edible MIPs): a marijuana-infused product that is to be consumed by eating or drinking.

Non-edible Marijuana-Infused Products (non-edible MIPs): a marijuana-infused product that is to be used through routes other than eating or drinking (i.e., all other uses).

Examples: This column identifies common product-type examples and is not considered an exhaustive list.

Type: This column provides fields to describe further product-type classification. Examples of Types by Category are provided in the Examples column (e.g., finished flower, pre-rolls, "mini"-pre-rolls, etc.).

Description: This column provides fields to include a product description describing characteristics such as appearance, intended route of use, and instructions for use (e.g., suggested serving size).

Product Weight: This column provides fields to include the product weight (e.g., net weight) by unit of sale (e.g., a single serving edible MIP: 100 grams)

Dose/Potency: This column provides fields to include the product cannabinoid dose for each advertised cannabinoid in amounts, expressed as the dry-weight percentages or milligrams of Δ^9 - tetrahydrocannabinol (Δ^9 -THC), cannabidiol (CBD), tetrahydrocannabinolic acid (THCa) and cannabidiolic acid (CBDa) in a medical marijuana product. Amounts of other cannabinoids may be reported, but are not required.

Retail Price: This column provides fields to include the estimated retail price (US dollars) for the specific product described. Itemized prices are most useful but a price range may additionally be provided to capture market variability and other closely related products.

Appendix C: 2015-2016 Cohort Patient-Reported Negative Effects

Note: Word choice and spellings have been retained as written by respondent to avoid inadvertent mischaracterization of intent. Brackets have been used to explain words redacted to prevent individual identification or for other reasons. Negative effects are broken down negative effect type, and by negative effect score rating.

Access-Related Issues

No Score

- Can use cannabis as in a group home
- Travel to get the product

1: No Negative Effects

- none, other than difficulty/inconvenience in accessing medical cannabis
- I have to ride 3 to 3 1/2 hours one way for my medicine because there are none in southwest Minnesota.
- The only issue is the distance I need to travel to get it if I don't take into account the cost
- I have to ride 3 to 3 1/2 hours one way for my medicine because there are none in southwest Minnesota.
- the only negative effect i have experienced is when i had to find a Doctor that would certify me. All my health care providers were told not to participate in the cannabis program. Finally my Doctor was able to certify me. Also the self exam questions when getting the medical cannabis from the dispensary are useless.
- Locations of dispensaries. We have to drive from [CITY] to the cities.

2

- Travel to pick up my prescription.
- Difficulty accessing medical cannabis
- Time consuming to order, drive and pick up medicine.
- unable to use outside of the state of MN.

3

- Physically having to pick up medication by myself

4

- The fact that my son's home care nursing staff is not permitted to administer PRN or scheduled Medical Cannabis is a difficult component at times.
- Driving so far away to get meds. And [CANNABIS PATIENT CENTER] not being open as much!!!

7: Great Deal of Negative Effects

- Distance.... DISTANCE.

Physical Negative Effects

No Score

- tired
- Did not like inhaling the cannabis. Irritated my lungs.
- a moderate dry mouth.
- seizures worsened but unsure if completely related to medical cannabis

1: No Negative Effects

- Dry mouth , and too many trips to the fridge
- some nausea after capsule form.
- I experience fatigue but that is a plus because I had problems sleeping at night because of pain. it seems to help with that
- sleep
- Cotton mouth!
- Stomach upset only when not taken with food.
- slight fatigue
- Mild drowsiness
- Do you feel a little tired at times .
- Sometimes my mouth can become dry, but it's fine if I'm hydrated.

2

- Had a bad reaction to oil suspension, this was corrected by adjusting dosage
- Initial increase in seizures
- We noticed the combination of CBD/THC worsened seizures for [PATIENT]. CBD also seems to be upsetting on her stomach with changes/increases in dosing.
- Getting chest colds from vape pen.
- e-cig- too much inhaled caused excessive coughing and vomiting.
- more small seizures
- sore throat
- fatigue
- Yes ~ In the morning I have to be careful with my blood pressure. It does lower it a bit. I have to watch my fluid intake because of my cathing schedule. Plus I already have low blood pressure in the morning. This lowers it a bit. I'm finding I need to drink Gatorade and get up a bit slower and then I'm fine. But out all the benefits this side effect is so minor and manageable. I could go into the crazy cost, the monthly travel time from [CITY] and having others pick it up for you without having to pay for another background

check when the company they work for through you already did one. I shouldn't have to pay for another PCA criminal background study for a current PCA that works for me. That is redundant request. Suggestions: Could there be a 3 month supply given instead of a 30 day supply? This would eliminate some winter driving months, gas money and for people who are suffering in pain (dying of cancer or children having seizures) it's so hard for them to travel. Some days even hard for them to get out of bed or eat. I wish people understood. I wish people would be more compassionate. People hurting ~ suffering are willing to pay for this with in reason, travel within reason and doctors are willing to come on board but without fear (so I don't blame them). I do not feel it's fair to ask a question on negative effects of a drug without asking the positive and negative effects of the process too! I am only one voice but today please allow me to be the voice of many...

- Increased appetite- causing weight gain
- Some head shaking as side effect.
- bad aftertaste with vaped oil
- Dry mouth
- Increased appetite.
- Dry mouth, and the need to carefully plan when I'm going to take the Cannabis so it doesn't interfere with daily life
- dry mouth
- seems to sleep more. Can not respond to other examples given as [PATIENT] does not have a form of communication that pertains to pain or depression, confusion, etc...
- Tired
- Coughing. Headache
- heaviness in legs
- Sometimes the pills make me too tired and I sleep more than I would like.
- Munchies : (
- with the vapor only, bad taste
- I really dislike the taste from the vape pen.
- We have experienced the occurrence of night terrors which we have not seen prior to starting medical cannabis. We are uncertain if this is related to the medication or a normal developmental step.
- speed of effects and lasting time.
- He just gets a little tired, he ever it doesn't both either of us and I love that it's 1pp% natural!
- slight dizziness and mental cloud
- Some stomach upset.
- Tired
- Smell from vapor pen can cause nausea.
- Tiredness
- 1. Sleepiness/tiredness

2. Hard to regulate dosage on vapor pen, can become paranoid if too much inhaled
3. Can hurt lungs and cause coughing if inhaled too hard, after learning how hard to inhale it has been much better.

- Sometimes the cannabis in oral liquid makes me a little queasy.
- I have gastroparesis with a stomach implant. I found when taking the heather solution it caused constipation.
- Like to rest a moment after vaping a dose.... but just time my day accordingly.
- The vaping can cause congestion, and you already have that going on because of the Chemo.

Some fatigue, but it's once you have been up and moving, so it's not so bad that it causes you to rest from time to time.

It's hard to know if mental clouding is caused from the chemo or the cannabis. However it's not enough to be alarmed.

- Very sleepy if I don't go to bed in a timely matter after my evening dose.
- Fatigue

I have some mental clouding but partly from the effects of chemo

- 1. Increased Heart Rate
2. Sweating and Heat Flashes
 - Dry mouth the cost is very high
 - Feel sleepy so I have to time taking the medications (vape or tincture). It is expensive also so I can't get a refill as easily as I would like since money is tight because of my conditions anyways.
 - Sluggish next morning
 - To strong
 - When on [HIGH CBD PRODUCT], loss of coordination and had increased weakness.
 - Fatigue was an initial issue, but medication adjustments have brought it under control. I don't like having to complete the survey every time I refill, it should be mandatory a couple of times a year and self elective if great improvements or noticeable worsening of issues.
 - Only side effect is diarrhea at times
 - Dry mouth
 - Lethargy
 - Stomach rumbles after taking the pill
 - Maybe increased the appetite
 - tired
 - Occasional tired, that could also be attributed to the chemotherapy
 - dry mouth and dizziness
 - While taking the tincture product I got a headache.
 - sluggish/drowsy, occasionally
 - I haven't been able to tell if from the vapor or pill but I've noticed increased drowsiness.

3

- initially makes me worse.
- possible drug to drug interaction
- Saw great results with Violet, but when we added Indigo at night, [PATIENT]'s sleep/wake cycles were disrupted. 3 weeks in a row after adding [HIGH CBD PRODUCT] he would stay awake for 24 hours, then sleep for 24, & it would take a few days before he could get back on track. That was the only change we made so I think the very small amount of THC in it had adverse effects for him. Went back to [HIGH CBD PRODUCT] only.
- A little off balance if taken when awake
- Nondry mouth
- coughing and dry throat upon taking. [MANUFACTURER] inhalers worse than [MANUFACTURER] spray but still have bit from spray.
- May be contributing to frequent loose stools
- It takes 1-2 hours for the oral medical cannabis to kick in. My throat sometimes gets sore after using the vaporizer.
- Mostly positive. Maybe a bit tired sometimes.
- Tiredness But that's in combination with other seizure medications that he takes
- I just notice that I cough more using the vape pens vs the oil
- [PATIENT] is dead. I can't answer this question in detail. He was not able to communicate much at the end. But I remember him expressing that he did not like the taste.
- cotton mouth
- upset stomach
- seem to be more tired
- Regulating the correct amount and type correct which takes time and experience. Much easier to do with the pills it seems for me personally as smoking it made my lungs worse and often times would be hard for me to control the dosage.
- I would like more edible options

4

- Interaction with other five seizures medications is hard to identify.
- while the cannabis helps with the muscle spasms, it seems to make my nerve damage worse.
- Drowsiness
- Makes me sleepy if I take during the day.
- I have experienced occasional diarrhea from using the oral suspension product.
- speaking quite loudly at home since starting the product
- fatigue
- Reduction in morning energy levels.
- Unsteadiness

- I don't like the side effect that gives me the munchies, I have a weight issue and it makes it hard for me to use it often.
- the oil in higher doses seem to cause me some small belly issues >but I do need it to calm pain/ spasms at night so I can sleep.
- dizziness
- Nausea
- symptoms seem to go up and down as the body adjusts to the cannabis and can be frustrating. still adjusting dose to find what will work best so still having symptoms/tics. can cause both hyperness and sleepiness
- Weight gain
- Sleepiness
- I tend to sleep a longer some days, but the days I am awake I have more energy and I feel better than I have in a long time. I have also lost about 8 lbs. since I started in the program.
- Little tired
- It gives me a sore throat and it tastes really bad
- Fatigue
- increased appetite
- Blurred vision
- Dizziness
- some headache
- I'm a little more tired and eat more
- Constant hunger

5

- increased seizure activity
- possible allergic reaction; i.e., hayfever - type symptoms
- Has interacted with my other seizure meds
- The oil made me sick
- Lightheadedness
- Vaping really hurts my throat. And since there is no raw flower available to purchase, I'm stuck with a sore throat. The oral options don't take effect for an hour or two, and even then, they don't relieve my symptoms effectively like vaped or smoked. I hope raw flower is available soon. I bet it's even safer than vaping.
- visual impairment
- Terrible headaches
- Dry mouth
- Notice I tend to eat more which leads to weight gain, sleepiness

6

- More seizures

- Sublingual tincture seems to be very caustic to the soft tissue under the tongue
- My son's seizures got worse when we moved from CBD only to [HIGH CBD PRODUCT]. It could be a coincidence, but even after I stopped the oil, I could not get his seizures under control and we had to be admitted to the hospital
- stomach pains
- sleeping
- Shakiness, balanced worsened
- I have stopped the cannabis. While the cannabis helped, I have had two spells of light-headedness and almost passing out. It would appear they are caused by the cannabis
- Dizziness and once passed out

7: Great Deal of Negative Effects

- Caused pain on left side of body
- Tried several times to restart with just one kind then the other
- still pain
- Found that I am allergic to cannabis - I broke out in hives approx. 6 weeks after starting to use it. Now, after 9 weeks off of it, the hives are almost gone.
- Severe, uncontrollable diarrhea. Severe, rapid weight loss. Increased seizure activity due to extra stress on body caused by severe, uncontrollable diarrhea and weight loss.

Mental Negative Effects

No Score

- b in the question below

1: No Negative Effects

- Anxiety increases on occasion.
- None-just cloudiness sometimes
- felt buzzed twice

2

- The most irritating part of the program is we have to do oil. I have never liked oil because it makes my short term memory a little worse and gives me mental clouding. It's not that big of a problem but I get annoyed if I forget something or I'm not thinking at my full ability. I had never had any negative side effects when I smoked the plants buds. In my experience oils good if you want to get high. But for treating crohns smoking the plants buds are better. This is because bud contains other chemicals than just thc or cbd that help with crohns while oil doesn't. This rule makes absolutely no sense. I understand that this was made law because someone who was ignorant in regards to cannabis thought ""vaping oil"" sounded better than ""smoking bud""
- But please please please fix this stupid law and let me treat my crohns with no negative side effects again.

- The fact that the oil makes me too high, mellows me out too much; regular cannabis lets me function on a normal level
- I need to time my dosage at night so I don't feel groggy in morning.
- Some decrease in motivation.
- Generally makes me feel lousy. I couldn't function even with a small dose.
- Slight memory loss (short-term memory)
- Very rarely happens, but losing train of thought when making a point. Now practicing my own "tickler techniques" to get my thought pattern quickly back on track.
- The high, it's not bad but I only use at night
- just a couple of times feeling high.
- At first, I had to try the different cbd/thc formulas. There were some times when I felt confused or lightheaded. Now, I know what blend to take to address my symptoms and I've figured out which delivery method works best for me. Now I have almost no negative effects.
- Would prefer not feeling altered and sometimes vapor pen doesn't seem to be releasing and I take in more than planned - very short term impact.
- At first it made my head feel a little funny, but very quickly that has gone away and having less pain has been a huge improvement. I have many more good days.
- nothing significant noticed. maybe some slight ""mental cloudiness"" but not every time and very mild
- Getting stupid.
- Short term memory loss.
- Forgetfulness/Losing train of thought
- Some confusion
- using the cbd oil, at times I have felt out of it.

3

- Makes me lazy.
- I cannot take any cannabis with THC in it. Must take only pure cannabis. With the THC I get anxiety. With out is everything is good
- depression
- Loss of judgment.
- In the beginning he seemed very lethargic, now that is better but [PATIENT] still has lack of appetite often
- Makes me feel rather lazy - I try to use that to my advantage and catch up on some sleep or to relax.
- unmotivated, subdued, weak and tired if too much THC - still trying to find that right balance
- Unable to drive for four hours after taking.
- Not being able to drive when using the cannabis
- Some mental clouding for about 2 hours

- mental clouding
- mental fog
- Some cognition fog that seems to decrease with time.
- Gotten almost lazy

4

- Increased anxiety, but I could still be detoxing from clonazepam. Today has been better.
- Hyper and Impulsiveness
- Disorientation
- Getting high
- Struggle with memory, focus, comprehension, weight gain, staying on task, lose track of time & easily distracted. Which affects my work....however it helps with my intense pain & migraines, which is why I wanted to take it..
- It has added to my cognitive confusion/fibro brain symptoms at times. It does a really good job of masking the pain I get from physical exertion which has been a downside because then I've over-done at times which then has added to my fatigue and exhaustion and pain. Prior to the MM, my pain was my greatest problem. Now that the pain has been managed to a better extent, I now am dealing with overwhelming fatigue and exhaustion a lot of the time.
- Balancing previous existing mental health issues.
- If I use enough to better "control" pain, I can get paranoid. It can also cause urinary retention, but other times, it helps me to go.
- I do not feel like myself
- Anxiety, chills, sometimes fatigue and/or confusion, sore throat/coughing from vaporizer
- High feeling
- increased sedation, lightheadedness
- social anxiety not wanting to be around people when I'm on the medicine
- makes me loopy
- Small amount of paranoia
- High feeling
- Uncooperative
- I've felt depressed and sad and wanting to be in the dark liking it to be very silent and also not wanting to be around others.
- I'm not effective or efficient when I'm using cannabis. I'm awake, but impaired. When I've had to use different things in the past like opioids, I'm ineffective, but I'm usually asleep the whole time. Being awake and impaired, I spend a lot of time confused and unable to follow conversations, read or watch TV. Cannabis doesn't make me sleepy.

5

- anxiety
- it's difficult to take it during my work hours, because it makes me feel less attentive, NO pain or pain.
- When taking it sometimes, maybe a little paranoia set in. That is something I can't have.

6

- Crying and irritability non stop once we increase the dose from 1 ml to 1.2 ml.

7: Great Deal of Negative Effects

- change in behavior and mood, digestive/pancreas?/liver? upset
- not aware of day/time, not remembering what I was saying mid-sentence, increased anxiety

Cost-Related Negative Effects

No Score

- the hardest part for me is the cost. I wish it was covered by insurance. Our insurance premiums are so high and then the additional cost for this just puts us up over the edge in costs...which depresses me.
- Was only on med. cannabis for 4 days and had to quit due to other medical issues and cost!

1: No Negative Effects

- Cost
- The cost! !!!!!
- I'm not allowed to list financial cost
- cost
- The cost is outrageous
- cost
- cost
- Cost price availability
- None beside cost
- Cost
- The cost is so much that i think in time people will search out other otions
- The cost is very high ! Have to find a way to lower it ???
- expensive
- Cost and accessibility I live in northern mn
- The price and not available in leaf form.
- None, except expensive
- Cost is unreasonable
- None..just the cost

- Cost..., way too much.
- Just cost and lack of ability for [PATIENT]'s MA Tefra to help us with the out of pocket expense.
- can't afford to try a more therapeutic dose have to drive 180 miles round trip to the dispensary
- Cost of Medicine
- Cost and way of consuming. THC oil is 70%. Plant matter is 20-25%. Hundreds of other elements in the cannabis plant besides THC, CBD that is useful consumption. Some want the cannabis glowered bud to consume in smoking or edibles extracted from the cannabis buds.
- The price.
- cost
- The cost of the medicine. The extract version of the cannabis plant is definitely more potent than loose leaf cannabis. However, the introduction of lower cost leaf cannabis would help patients afford the medicine.
- The cost of the cannabis and it NOT at all whatsoever being covered by insurance it is medicine just as any other medicine.
- none just cost
- The cost
- Cost
- cost!
- None beyond funding.
- the cost of medication is high for someone out of pocket with out insurance paying for it
- None, no negative effects ., only the cost has been a factor as it is not covered by medical insurance and it is too much money and is hard to afford.
- cost
- Besides cost, nothing is negative.

2

- The cost for a young person. Insurance does not cover it.
- cost, or lengthy road trip to dispensary
- Price
- The cost is high and month to month I do not know if I will be able to afford a monthly supply.
- cost

3

- cost
- The cost of the product is crazy high and not in line with the market. The same product in WA, CA, or CO costs about half of what things cost in MN.

4

- Cost (2 reports)
- Financial. It is very expensive. That is the only negative.

5

- Cost

6

- Way too expensive where I can't afford it!
- money that is charged

7: Great Deal of Negative Effects

- I'm broke and still need medicines that other states get at a much lower price. I lied and borrowed just for my first time. It's hard buying not know for sure that's what I want or need. Purchased unless items.having a choice between strain IE sour diesel, headband,kush and etc.
- would rather suffer than go to mn med solution again, thy are worse thieves than the drug dealer down the street. leafline lab was ok.

Negative Attitudes Toward Medical Cannabis Use

1: No Negative Effects

- the only negative effect i have experienced is when i had to find a Doctor that would certify me. All my health care providers were told not to participate in the cannabis program. Finally my Doctor was able to certify me. Also the self exam questions when getting the medical cannabis from the dispensary are useless.
- what other people would think if they know- so I don't tell them
- The only negative impact would be not telling anyone what is turning my health around because of the views of some people with cannabis.
- Poor reception to cannibis at [HOSPITAL]. Serious lack of staff knowledge and support.

2

- The nay-sayers tire me out. Two [HOSPITAL] employees (my sister/aunt of my son and a [HOSPITAL] doctor friend of our family) insisted that there is no proof that medical cannabis helps. "You might as well give your son dirt". Was a comment I heard from the [HOSPITAL] MD friend. I typically, patiently, point out that our son is on 4'heavy duty anti seizure medicines, has been most of his life, that can't be increased due to ill effects, has a VNS, yet is still slammed to the ground, on to his face, from seizures many times a day, or can't breath for up to 30 seconds during a tonic seizure. So are we not to try anything that might help?! Now, 3-months in to starting medical cannabis, I can show anyonemwho,asks how,it is,going his seizure diary, where there are far fewer entries for daily seizures. Just a glance at my son's monthly calendar these past 3

months tells it all. Is medical cannabis perfect? No, it is not as fast acting as anti seizure mess (for those that work), it is a very slow process, ramping up the oil, trying to get it just right. The beauty of medical cannabis is that we are seeing no negative side effects! No shortening of his QT waves, no lowered white blood cell counts, no rage and attacks on family. Just a slow improvement on seizures, making all of our lives so much easier.

- People laugh when I tell them I'm trying Medical Marijuana. No one believes it can help they believe it's only recreation. The only people that understand are people like me that have run out of options.
- Public opinion.
- Stigma of MJ
- I have only shared that I use cannabis to very few people. One person shared her (negative) opinion. I let go of her.
- The only negative effect is the possible stigma that I face from using, what most people consider, a drug.
- Getting over the stigma of marijuana use in society. I.E. Some family members don't approve.

3

- New neighbors felt that it wasn't right for anyone to use medical cannabis.

4

- Care providers, other than my registered provider, that are apprehensive to participate in the program. Lack of education, wide spread communication in the medical community regarding the benefits and laws regarding medical cannabis in MN.
- Medical communities (hospitals) need to be educated on medical cannabis. We were not allowed to bring into the hospital
- embarrassment taking treatment with others around.

5

- People saying that I am on drugs
- Doctors don't want to treat medical cannabis patients. Cost.

Other Negative Effects

No Score

- Need more distributors

1: No Negative Effects

- It hasn't worked to stop her seizures
- any breakthrough seizures. [PATIENT] had 3 in November, yet none this month as of this writing.
- Not able to use it. Didn't like it and did not feel relief

- the same amount does not always have the same effect every time
- Wish it worked better.
- The pen leaks??
- not having proper bottle caps for liquid cannabis
- Running out month ago I have not been able to function
- OTHER TREATING PAIN CLINIC IS PROHIBITING USE OF MEDICAL MARIJUANA SO I HAVE BEEN UNABLE TO TAKE IT THE LAST 30 + DAYS
- I wish they could leave more of the recreational in the pot, it helps me forget that I have MS for a while, and street pot does this I think it's part of the therapy. So I am having a hard time giving up my street pot.
- Maybe if they add more so it can last longer it leaves so quickly even if I measure the time.
- A negative impact of having only THC and CBD products is that they aren't as effective as natural whole plant cannabis.

2

- Not fully effective
- Seizures cluster after 7 days or so and she gets tired too.
- Inconsistency of seizure activity.
- It took several tries to find an appropriate dosage and combination to work at minimizing tics.
- It has not helped the increased ammonia level [PATIENT] has had the past few years. With the direction of his neurologist, we are currently weaning off one of his seizure medications, depakote, which he has been taking for 26 years! We are hopeful that this may help reduce the ammonia level.
- Haven't been able to find the right form of treatment (Suspension/Vape/Pills) that works best for me.
- Prefer the oil but trying to utilize the syringe with my fingers is really tough! Would really like it if I could administer the oil myself with a different tool.
- I would like to have a type for bedtime. I can't always get to sleep and while I have cut down my 2 50mg a night Trazadone to one one 50mg maybe 3-4 times per week.
- Trying to determine correct dosages.
- I can't get other medicines due to being on this program.
- Having to take the medicine several times per day.
- having to refrigerate pills. if the tincture does not require refrigeration, I may try that...
- Program does not allow enough "options" or other products..VERY limited

3

- I do not want to drive after using medical cannabis for fear of being arrested for DUI even if I can pass the roadside sobriety tests because my blood has THC in it and I could

be charged with DUI just from using medical cannabis even if I have not used it for days before driving.

- Worry about changing jobs/company due to drug testing
- Im worried about my employer or future employment drug testing
- Regulating the correct amount and type correct which takes time and experience. Much easier to do with the pills it seems for me personally as smoking it made my lungs worse and often times would be hard for me to control the dosage.
- I would like more edible options

4

- I have more anxiety that police may take me for a blood test of charge me with DUI if they know I'm a patient at dispensary. I also had a Warning of illegal drug use in a urine test from the so called pain clinic I'm required to go to by [CLINIC] By my now ex primary Dr of 20 years. I told the pain clinic when I signed contract not to use illegal drugs that I took cannabis by prescription in medical form thru Dept of Health etc. The Dr said OK, as long as it wasn't in organic form for smoking! He said I was the 1st patient at [CLINIC] to be on legal cannabis. I advised him, I maybe to 1st but surely not the last patient. They said this will be resolved ok but I still was warned for illegal thc drug use, which is upsetting but it will be straightened out. Thank u!!
- The stick does not always work
- I have sciatica nerve pain, and don't get as much pain relief for that. Also, it is hard to get the dosages down right so that a steady stream of it stays in your system. I mainly use the gel caps.
- No help with seizures.
- As an adult with muscle spasms I need [HIGH CBD PRODUCT] or maybe even [HIGH CBD PRODUCT], I would like to have a broader range of treatments on the CBD CBD range. I understand that this is more for children, but vaporizer for adults would be wonderful. I can not take pills due to stomach problems. I do have vaporizers to help with pain, sleeping issues due to spasms. Please consider more CBD CBD VAPORIZERS for adults.
- Some negative ONLY because of the MCT, not the cannabis it self! Why do they add such an expensive product like (MCT) to something when it could be more reasonably priced without it??? I had to really do my research on MCT to know what this awful stuff can do. There is blog after blog with people complaining about MCT. There are people out there that have not done their research and think it is the cannabis. It is really too bad because they could really benefit from the cannabis without the MCT. Again it would be cheaper without the MCT in it.
- Variations in batches.
- Not quite strong enough or
- could use more

5

- Continued loose to diarrhea stools.
- Because certain types are not available yet, i haven't been able to try all of the varieties. Having all of them available may give patients better options as to what works best, especially in the first few months. I experience both muscle spasms and chronic pain, and have seen benefit from [1:1 THC:CBD PRODUCTS] and occasionally [HIGH THC PRODUCT]. But I do wonder if one of the other colors would work longer.

6

- Mixed strains make the medication unreliable. Made him very sedated and "high" acting even at very low doses.

7: Great Deal of Negative Effects

- My ex using it as an excuse to get custody of my children
- Seizures are the same and mobility is still down. She walks and sits hunched over:(

Minnesota Department of Health
Office of Medical Cannabis
85 E 7th Place, Suite 220
PO Box 64882
St. Paul, MN 55164-0082
651-201-5598
health.cannabis@state.mn.us
www.health.state.mn.us

10/11/19

To obtain this information in a different format, call: 651-201-5598.

Benefits Reported on the Patient Self-Evaluation: Patients with First Enrollment July 2015-June 2017

Summary

Of patients included on the standard 8 symptom analysis (n = 6924), more than half experienced moderate to severe symptoms at baseline on all measures except for nausea (49%) and vomiting (23%). Of patients experiencing moderate to severe symptoms at baseline, anywhere between 33% and 66% achieved at least a 30% reduction in symptom severity (symptom improvement) within 4 months of their first medical cannabis purchase. The lowest proportion of patients reporting symptom improvements in the initial 4-month period were for pain (33%) and fatigue (44%) symptoms, while the greatest proportion of patients reporting symptom improvements were for vomiting (66%), nausea (60%), depression (59%), and lack of appetite (58%) symptoms. Similarly, a smaller proportion of patients were able to maintain those symptom improvements in the following 4-months for pain (41%) and fatigue (50%) symptoms compared to all other symptoms (maintained anywhere by 56%-66% of patients).

Benefits Reported on the Patient Self-Evaluation: Patients with First Enrollment July 2015-June 2017

The patient self-evaluation is required for patients to complete prior to each medical cannabis purchase. It includes questions to assess symptom severity, some of which are administered to all patients (standard set of 8 symptom measures) and some of which are tailored to symptoms for a given condition (condition-specific symptom measures). Since symptom data is collected prior to each patient's first medical cannabis purchase, symptom changes can be assessed over time and compared to baseline (baseline = patient responses to symptom questions just prior to their first medical cannabis purchase).

Standard 8 Symptom Measures

The standard 8 symptom measures that all patients receive are answered on a 0-10 numerical rating scale (NRS), with 0 indicating absence of the symptom to 10 indicating that the symptom is as bad as the patient can imagine (see Box 1). Therefore, higher scores on these measures indicate poorer management of these symptoms. Patients are asked to rate symptom severity over the past 24 hours.

Box 1. Listing of the Standard 8 symptom measures that all patients answer, including the response options available to patients.

<u>Standard 8 Symptom Measures:</u>										
Anxiety					Fatigue					
Lack of Appetite					Nausea					
Depression					Pain					
Disturbed Sleep					Vomiting					
<u>Response Options (0 – 10 NRS):</u>										
0 1 2 3 4 5 6 7 8 9 10										
Symptom not present					Symptom as bad as one can image					

To understand whether patients derived any symptom benefits during their participation in the program, the following two questions were explored for each Standard 8 symptom measure:

QUESTION 1

Of those patients who experienced moderate to severe symptoms at baseline (score of 4 or higher at baseline), what percentage of them experienced at least a 30% improvement in symptoms within four months of their first medical cannabis purchase? The threshold of $\geq 30\%$ reduction on a 0-10 point scale was chosen because this threshold has been documented in clinical trials to represent clinically meaningful change – especially for pain reduction and spasticity reduction. Examples of $\geq 30\%$ change include moving from a score of 10 to a score of 7, from 9 to 6, from 8 to 5, from 7 to 4, etc.

QUESTION 2

If a patient achieved at least a 30% improvement on symptoms within 4 months of their first medical cannabis purchase (determined in Question 1), what percentage of them will, on average, still maintain that level of improvement in the four months following that initial 30% symptom improvement? [Four-month follow-up period]

Results on Standard 8 Symptom Measures

See Table 1 for results. The third column displays the percentage and number of patients (out of 6924 patients) experiencing moderate to severe symptoms at baseline (baseline response ≥ 4) on a given Standard 8 measure. Fourth column represents answer to Question 1: percentage (and number) of moderate to severe scorers at baseline who achieved at least a 30% symptom improvement at any time within 4 months of their first medical cannabis purchase. Fifth column

BENEFITS REPORTED ON THE PATIENT SELF-EVALUATION: PATIENTS WITH FIRST ENROLLMENT JULY 2015-JUNE 2017

shows the number of patients that had submitted symptom data during their designated 4-mo follow-up period (4 month time window that followed their initial symptom improvement). Symptom responses during this 4-mo time period were averaged together within each patient. The sixth column shows the percentage and number of patients who had achieved $\geq 30\%$ symptom improvement that had – on average – maintained at least that level of improvement in the 4-month follow-up period. Lastly, the seventh column shows the percentage of all patients who both achieved at least a 30% improvement in the first 4 months since their first medical cannabis purchase and maintained that improvement on average in the 4-month follow-up period.

Table 1. Overall Standard 8 Symptom Results (n = 6924).

All patients collapsed across conditions (n=6924)

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	76.1 (5270)	56.4 (2972)	2449	58.0 (1724)	32.7
Appetite Lack	56.3 (3900)	57.9 (2257)	1879	60.1 (1357)	34.8
Depression	65.2 (4511)	59.2 (2672)	2204	59.5 (1589)	35.2
Disturbed Sleep	88.3 (6116)	54.9 (3358)	2829	56.1 (1885)	30.8
Fatigue	92.4 (6401)	43.6 (2791)	2366	49.7 (1388)	21.7
Nausea	48.5 (3361)	59.5 (2000)	1660	61.9 (1237)	36.8
Pain	93.8 (6497)	32.7 (2124)	1783	40.8 (866)	13.3
Vomiting	22.7 (1571)	65.6 (1031)	830	66.1 (681)	43.3

Results on Standard 8 Symptom Measures Stratified by Qualifying Condition

Tables 2-11 below shows the responses to the standard 8 symptoms stratified by qualifying condition.

Table 2. Standard 8 Symptom Results in Patients with Intractable Pain (n = 4060).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	76.5 (3107)	58.2 (1809)	1563	58.6 (1060)	34.1
Appetite Lack	51.8 (2102)	62.2 (1307)	1140	61.6 (805)	38.3
Depression	66.2 (2689)	61.1 (1643)	1413	59.9 (984)	36.6
Disturbed Sleep	90.6 (3677)	57.3 (2107)	1831	56.5 (1190)	32.4
Fatigue	93.4 (3793)	45.7 (1735)	1531	49.8 (864)	22.8
Nausea	44.5 (1808)	64.3 (1163)	999	61.6 (716)	39.6
Pain	99.6 (4045)	29.4 (1188)	1076	35.8 (425)	10.5
Vomiting	18.5 (752)	71.8 (540)	454	70.0 (378)	50.3

Table 3. Standard 8 Symptom Results in Patients with Muscle Spasms (n = 1403).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	80.2 (1125)	58.0 (653)	543	58.5 (382)	34.0
Appetite Lack	57.0 (800)	62.0 (496)	422	63.1 (313)	39.1
Depression	67.1 (941)	60.9 (573)	483	61.6 (353)	37.5
Disturbed Sleep	90.2 (1266)	53.0 (671)	586	58.7 (394)	31.1
Fatigue	92.7 (1301)	44.6 (580)	502	53.1 (308)	23.7
Nausea	47.9 (672)	65.5 (440)	378	65.5 (288)	42.9
Pain	95.8 (1344)	35.7 (480)	424	46.7 (224)	16.7
Vomiting	23.6 (331)	69.8 (231)	195	71.0 (164)	49.5

Table 4. Standard 8 Symptom Results in Patients with Cancer (n = 1029).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	74.8 (770)	43.5 (335)	259	56.7 (190)	24.7
Appetite Lack	77.4 (796)	38.4 (306)	237	51.0 (156)	19.6
Depression	66.7 (686)	45.9 (315)	239	54.6 (172)	25.1
Disturbed Sleep	85.4 (879)	42.3 (372)	285	48.4 (180)	20.5
Fatigue	94.7 (974)	26.6 (259)	211	40.5 (105)	10.8
Nausea	65.7 (676)	37.9 (256)	197	55.9 (143)	21.2
Pain	89.1 (917)	30.0 (275)	207	40.4 (111)	12.1
Vomiting	36.2 (373)	46.9 (175)	133	58.3 (102)	27.3

Table 5. Standard 8 Symptom Results in Patients with Seizures (n = 506).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	70.8 (358)	67.3 (241)	211	67.6 (163)	45.5
Appetite Lack	49.0 (248)	74.6 (185)	161	71.4 (132)	53.2
Depression	55.7 (282)	74.1 (209)	180	70.8 (148)	52.5
Disturbed Sleep	79.2 (401)	68.3 (274)	245	61.7 (169)	42.1
Fatigue	84.2 (426)	62.0 (264)	241	59.1 (156)	36.6
Nausea	44.3 (224)	74.1 (166)	149	75.9 (126)	56.3
Pain	64.2 (325)	58.2 (189)	168	63.0 (119)	36.6
Vomiting	25.5 (129)	79.1 (102)	92	77.5 (79)	61.2

Table 6. Standard 8 Symptom Results in Patients with Inflammatory Bowel Disease, including Crohn’s Disease (n = 287).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	74.9 (215)	63.7 (137)	121	65.7 (90)	41.9
Appetite Lack	69.3 (199)	59.8 (119)	109	64.7 (77)	38.7
Depression	61.3 (176)	61.4 (108)	97	70.4 (76)	43.2
Disturbed Sleep	83.6 (240)	57.1 (137)	130	64.2 (88)	36.7
Fatigue	92.0 (264)	46.6 (123)	110	59.3 (73)	27.7
Nausea	69.3 (199)	66.8 (133)	112	66.2 (88)	44.2
Pain	91.6 (263)	49.8 (131)	116	55.0 (72)	27.4
Vomiting	31.7 (91)	73.6 (67)	63	77.6 (52)	57.1

Table 7. Standard 8 Symptom Results in Patients with Terminal Illness (n = 147).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	78.2 (115)	44.3 (51)	43	56.9 (29)	25.2
Appetite Lack	76.2 (112)	38.4 (43)	33	51.2 (22)	19.6
Depression	72.1 (106)	46.2 (49)	39	59.2 (29)	27.4
Disturbed Sleep	82.3 (121)	42.1 (51)	47	54.9 (28)	23.1
Fatigue	94.6 (139)	23.7 (33)	29	36.4 (12)	8.6
Nausea	61.9 (91)	45.1 (41)	37	65.9 (27)	29.7
Pain	91.2 (134)	20.9 (28)	21	39.3 (11)	8.2
Vomiting	34.7 (51)	52.9 (27)	24	55.6 (15)	29.4

Table 8. Standard 8 Symptom Results in Patients with HIV/AIDS (n = 90).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	85.6 (77)	44.2 (34)	31	70.6 (24)	31.2
Appetite Lack	73.3 (66)	50.0 (33)	29	63.6 (21)	31.8
Depression	66.7 (60)	48.3 (29)	26	75.9 (22)	36.7
Disturbed Sleep	88.9 (80)	46.3 (37)	32	54.1 (20)	25.0
Fatigue	83.3 (75)	41.3 (31)	25	48.4 (15)	20.0
Nausea	63.3 (57)	56.1 (32)	28	65.6 (21)	36.8
Pain	87.8 (79)	36.7 (29)	23	44.8 (13)	16.5
Vomiting	31.1 (28)	50.0 (14)	12	78.6 (11)	39.3

Table 9. Standard 8 Symptom Results in Patients with Glaucoma (n = 61).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	73.8 (45)	44.4 (20)	18	50.0 (10)	22.2
Appetite Lack	37.7 (23)	69.6 (16)	12	56.3 (9)	39.1
Depression	59.0 (36)	58.3 (21)	18	47.6 (10)	27.8
Disturbed Sleep	83.6 (51)	43.1 (22)	19	63.6 (14)	27.5
Fatigue	90.2 (55)	38.2 (21)	17	42.9 (9)	16.4
Nausea	32.8 (20)	45.0 (9)	7	66.7 (6)	30.0
Pain	83.6 (51)	41.2 (21)	19	42.9 (9)	17.6
Vomiting	16.4 (10)	60.0 (6)	5	83.3 (5)	50.0

Table 10. Standard 8 Symptom Results in Patients with Tourette Syndrome (n = 58).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	91.4 (53)	64.2 (34)	30	58.8 (20)	37.7
Appetite Lack	31.0 (18)	61.1 (11)	9	81.8 (9)	50.0
Depression	65.5 (38)	71.1 (27)	25	81.5 (22)	57.9
Disturbed Sleep	74.1 (43)	74.4 (32)	30	68.8 (22)	51.2
Fatigue	74.1 (43)	58.1 (25)	23	60.0 (15)	34.9
Nausea	17.2 (10)	90.0 (9)	8	66.7 (6)	60.0
Pain	56.9 (33)	63.6 (21)	20	71.4 (15)	45.5
Vomiting	5.2 (3)	66.7 (2)	2	100.0 (2)	66.7

Table 11. Standard 8 Symptom Results in Patients with ALS (n = 36).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	69.4 (25)	52.0 (13)	10	53.8 (7)	28.0
Appetite Lack	38.9 (14)	71.4 (10)	7	50.0 (5)	35.7
Depression	69.4 (25)	40.0 (10)	8	50.0 (5)	20.0
Disturbed Sleep	77.8 (28)	35.7 (10)	10	80.0 (8)	28.6
Fatigue	91.7 (33)	30.3 (10)	10	60.0 (6)	18.2
Nausea	30.6 (11)	63.6 (7)	6	71.4 (5)	45.5
Pain	75.0 (27)	48.1 (13)	12	30.8 (4)	14.8
Vomiting	8.3 (3)	66.7 (2)	2	100.0 (2)	66.7

Condition-Specific Symptom Measures

Besides the Standard 8 measures which are administered to all patients, some patients received additional symptom questions on the PSE to more adequately address condition-specific symptoms. These include, among others, questions on seizure frequency for seizure patients, questions on spasm frequency for muscle spasm and ALS patients, and Crohn's activity in Crohn's patients. While patients received the same response options on the Standard 8 measures (respond from 1-10 on a numerical rating scale), response options for condition-specific measures varied as indicated in Table 12.

All condition-specific measures were investigated within the same framework as the Standard 8 measures: 1) what percentage of patients achieved symptom improvement within the four months since their first medical cannabis purchase compared to their baseline responses, and 2) what percentage of those achieving symptom improvement showed general persistence in the 4-month follow-up period. A summary of results are similarly presented in a table like those presented for the Standard 8 measures (see Table 12 below).

Table 12. Results on Symptom Improvements on Condition-Specific Measures.

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Condition	Condition-Specific Symptom Measure	# of Patients Included in Analysis	% of Patients Achieving Threshold Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial Threshold Symptom Improvement	% of Patients Who Achieved Threshold Symptom Improvement that Maintained it**	% of Patients that Both Achieved Threshold Symptom Improvement and Maintained it**
Intractable Pain	Composite PEG Measure	3982	44.1 (1755)	1540	49.0 (860)	21.6
	<i>Pain Intensity</i>	3977	36.6 (1455)	1279	45.3 (659)	16.6
	<i>Life Enjoyment Interference</i>	3962	49.7 (1968)	1719	50.6 (995)	25.1
	<i>General Activity Interference</i>	3951	50.0 (1976)	1713	51.3 (1013)	25.6
Muscle Spasms	Weekly Spasms Frequency	1365	51.1 (698)	556	54.3 (379)	27.8
	0-10 Spasticity Scale	1292	40.1 (518)	443	45.6 (236)	18.3
Cancer: Cachexia/Wasting	Weight	345	11.6 (40)	29	45.0 (18)	5.2
Seizures	Weekly Seizure Frequency	469	62.5 (293)	245	66.2 (194)	41.4

Table 12 Continued. Results on Symptom Improvements on Condition-Specific Measures.

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Condition	Condition-Specific Symptom Measure	# of Patients Included in Analysis	% of Patients Achieving Threshold Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial Symptom Improvement	% of Patients Who Achieved Threshold Symptom Improvement that Maintained it**	% of Patients that Both Achieved Threshold Symptom Improvement and Maintained it**
Inflammatory Bowel Disease, Including Crohn's Disease	Subset of HBI Measures Combined	287	58.5 (168)	144	51.8 (87)	30.3
	<i># Liquid Stools</i>	111	56.8 (63)	52	65.1 (41)	36.9
	<i>Abdominal Pain</i>	192	59.9 (115)	99	44.3 (51)	26.6
	<i>General Well-Being</i>	52	59.6 (31)	25	35.5 (11)	21.2
	Weight	287	16.4 (47)	42	55.3 (26)	9.1
Terminal Illness: Cachexia/Wasting	Weight	51	21.6 (11)	8	45.5 (5)	9.8
HIV/AIDS	Weight	90	16.7 (15)	8	46.7 (7)	7.8
Tourette Syndrome	Weekly Tic Frequency	58	51.7 (30)	24	63.3 (19)	32.8
ALS	Weekly Spasms Frequency	33	39.4 (13)	10	46.2 (6)	18.2
	0-10 Spasticity Scale	23	21.7 (5)	5	80.0 (4)	17.4

Glaucoma patients were also administered their own condition-specific measure, which was to report on the most recent intraocular pressure test (IOP) result and the date the test was administered on each patient self-evaluation. However, rather than analyzing for changes on the IOP test compared to a baseline IOP result, these results are presented below as reported by the patients (see Table 13). All IOP test results represented to the left of the “First Visit” column indicate results from tests occurring prior to the patient’s first medical cannabis purchase; everything to the right of that column are results occurring after the patient’s first purchase. Column names refer to month in which the test was reported to occur prior to or after first purchase. Note that these results are not directly coming from the practitioner who administered the IOP test – reliance on patient documentation and/or memory is a limitation in interpreting these results.

Table 13. Patient-Reported Intraocular Pressure Test Results from Glaucoma Patients (n = 61): Left Eye/Right Eye.

* before first medical cannabis purchase

** after first medical cannabis purchase

Pat ien t	33- mo *	24- mo *	13- mo *	11- mo *	10- mo *	9- mo *	8- mo *	7- mo *	6- mo *	5- mo *	4- mo *	3- mo *	2- mo *	1- mo *	1- mo **	2- mo **	3- mo **	4- mo **	5- mo **	6- mo **	7- mo **	8- mo **	9- mo **	10- mo **	11- mo **	12- mo **	13- mo **
1				15 / 11														11 / 10		7 / 12							
2														20 / 17		17 / 14								18 / 16			
3														18 / 20	19 / 18			18 / 18		19 / 22	19 / 18						
4													26 / 28	26 / 28		18 / 18			18 / 16								
5														21 / 26													
6										20 / 20					20 / 20												
7														17 / 15													
8												34 / 30							33 / 33				26 / 24				

Table 13 Continued. Patient-Reported Intraocular Pressure Test Results from Glaucoma Patients (n = 61): Left Eye/Right Eye.

* before first medical cannabis purchase

** after first medical cannabis purchase

Pat ien t	33- mo *	24- mo *	13- mo *	11- mo *	10- mo *	9- mo *	8- mo *	7- mo *	6- mo *	5- mo *	4- mo *	3- mo *	2- mo *	1- mo *	1- mo **	2- mo **	3- mo **	4- mo **	5- mo **	6- mo **	7- mo **	8- mo **	9- mo **	10- mo **	11- mo **	12- mo **	13- mo **	
9														26 / 23	17 / 18													
10													30 / 30															
11										22 / 24	27 / 21	21 / 24																
12														12 / 10		12 / 12												
13														22 / 14	22 / 14													
14														9/ 26		8/ 12												
15													17 / 18		19 / 24													
16				22 / 20											16 / 16		17 / 17	16 / 16							18 / 19			

Table 13 Continued. Patient-Reported Intraocular Pressure Test Results from Glaucoma Patients (n = 61): Left Eye/Right Eye.

* before first medical cannabis purchase

** after first medical cannabis purchase

Pat ien t	33- mo *	24- mo *	13- mo *	11- mo *	10- mo *	9- mo *	8- mo *	7- mo *	6- mo *	5- mo *	4- mo *	3- mo *	2- mo *	1- mo *	1- mo **	2- mo **	3- mo **	4- mo **	5- mo **	6- mo **	7- mo **	8- mo **	9- mo **	10- mo **	11- mo **	12- mo **	13- mo **	
17														23 / 23	16 / 16	19 / 25	16 / 19	16 / 19					16 / 18					
18												10 / 12				12 / 15												
19														30 / 22		19 / 16		26 / 16										
20													17 / 19	19 / 17	19 / 17													
21														17 / 26	17 / 28		20 / 25				19 / 20						24 / 28	
22					13 / 14							12 / 13																
23			19 / 18											19 / 18				15 / 15										
24														12 / 15			14 / 14	12 / 12										

Table 13 Continued. Patient-Reported Intraocular Pressure Test Results from Glaucoma Patients (n = 61): Left Eye/Right Eye.

* before first medical cannabis purchase

** after first medical cannabis purchase

Pat ien t	33- mo *	24- mo *	13- mo *	11- mo *	10- mo *	9- mo *	8- mo *	7- mo *	6- mo *	5- mo *	4- mo *	3- mo *	2- mo *	1- mo *	1- mo **	2- mo **	3- mo **	4- mo **	5- mo **	6- mo **	7- mo **	8- mo **	9- mo **	10- mo **	11- mo **	12- mo **	13- mo **
25														16 / 16				14 / 14	14 / 14			14 / 13					
26														26 / 26													
27														10 / 12													
28													14 / 16														
29												25 / 25					16 / 16			16 / 14							
30												26 / 29															
31					22 / 21															22 / 21							
32														1/ 1			8/ 10										

Table 13 Continued. Patient-Reported Intraocular Pressure Test Results from Glaucoma Patients (n = 61): Left Eye/Right Eye.

* before first medical cannabis purchase

** after first medical cannabis purchase

Pat ien t	33- mo *	24- mo *	13- mo *	11- mo *	10- mo *	9- mo *	8- mo *	7- mo *	6- mo *	5- mo *	4- mo *	3- mo *	2- mo *	1- mo *	1- mo **	2- mo **	3- mo **	4- mo **	5- mo **	6- mo **	7- mo **	8- mo **	9- mo **	10- mo **	11- mo **	12- mo **	13- mo **	
33														16 / 30	12 / 19		9/ 19											
34														19 / 18			14 / 16											
35														16 / 14														
36													25 / 25						24 / 25			21 / 21						
37														24 / 25		24 / 23	22 / 22	19 / 19							19 / 19			
38												17 / 18	17 / 18								16 / 16							
39														17 / 17		14 / 8						14 / 8						
40		15 / 15													12 / 11			12 / 11										

Table 13 Continued. Patient-Reported Intraocular Pressure Test Results from Glaucoma Patients (n = 61): Left Eye/Right Eye.

* before first medical cannabis purchase

** after first medical cannabis purchase

Pat ien t	33- mo *	24- mo *	13- mo *	11- mo *	10- mo *	9- mo *	8- mo *	7- mo *	6- mo *	5- mo *	4- mo *	3- mo *	2- mo *	1- mo *	1- mo **	2- mo **	3- mo **	4- mo **	5- mo **	6- mo **	7- mo **	8- mo **	9- mo **	10- mo **	11- mo **	12- mo **	13- mo **	
41														20 / 21														
42													1/ 1		1/ 1	1/ 1				1/ 1								
43														12 / 12														
44											17 / 23			27 / 18										17 / 21				
45									21 / 16							18 / 15				15 / 18								
46				18 / 18													19 / 20											
47														20 / 19														
48	20 / 24																		20 / 24									

Table 13 Continued. Patient-Reported Intraocular Pressure Test Results from Glaucoma Patients (n = 61): Left Eye/Right Eye.

* before first medical cannabis purchase

** after first medical cannabis purchase

Pat ien t	33- mo *	24- mo *	13- mo *	11- mo *	10- mo *	9- mo *	8- mo *	7- mo *	6- mo *	5- mo *	4- mo *	3- mo *	2- mo *	1- mo *	1- mo **	2- mo **	3- mo **	4- mo **	5- mo **	6- mo **	7- mo **	8- mo **	9- mo **	10- mo **	11- mo **	12- mo **	13- mo **	
49														39 / 39			15 / 14											
50														12 / 12		16 / 15												
51														25 / 25														
52												17 / 17					18 / 18		16 / 14	12 / 14	12 / 11	12 / 11	12 / 11	12 / 11	12 / 12			
53								28 / 26																				
54														17 / 19			15 / 16				15 / 16				24 / 22			
55											23 / 23					17 / 19			15 / 16					21 / 21				
56				22 / 24																								

Table 13 Continued. Patient-Reported Intraocular Pressure Test Results from Glaucoma Patients (n = 61): Left Eye/Right Eye.

* before first medical cannabis purchase

** after first medical cannabis purchase

Pat ien t	33- mo *	24- mo *	13- mo *	11- mo *	10- mo *	9- mo *	8- mo *	7- mo *	6- mo *	5- mo *	4- mo *	3- mo *	2- mo *	1- mo *	1- mo **	2- mo **	3- mo **	4- mo **	5- mo **	6- mo **	7- mo **	8- mo **	9- mo **	10- mo **	11- mo **	12- mo **	13- mo **	
57														21 / 21							20 / 20	20 / 20						
58														25 / 23	23 / 19						16 / 18						16 / 18	
59														20 / 20	22 / 19		19 / 19		14 / 13			17 / 16	15 / 14			16 / 15		
60						18 / 25			15 / 18																			
61														15 / 15					18 / 18				20 / 20					

Caution is needed when interpreting the patient self-reported intra-ocular pressure results. It is possible that patients report incorrect values and dates of testing. Importantly, reported data provides little or no insight into changes in glaucoma therapies or other medications during the period after medical cannabis initiation. And, though we have record of which products are purchased when, without patient-level comparison of changes in product with changes in observed effect, we could miss differential impact of products. That analysis is beyond the scope of this report. With those caveats, we make the following summary observations.

After initiating medical cannabis use, 23 of the 61 patients (38%) reported intraocular pressure measurements with a decrease in intraocular pressure (IOP) ≥ 4 mm Hg in at least one eye, 18 (30%) reported no follow-up results in the year after medical cannabis initiation, and 20 (33%) reported follow-up values with no decrease in IOP ≥ 4 mm Hg (three had IOP decrease = 3 mm Hg in one eye).

Among the 23 showing a decrease in IOP ≥ 4 mm Hg, 17 reported more than one measurement during the year after following medical cannabis initiation. Among these 17 with multiple reported measurements, the ≥ 4 mm Hg decrease in IOP was present in the first reported post-initiation result for eleven (at months 1[x6], 2[x3], 3, and 4). In six patients, the ≥ 4 mm Hg decrease in IOP wasn't seen in initial reported result(s), but was present in a later result (at months 4, 5, 7, 8[x2], and 9). Among the six with only one post-initiation reported result, the ≥ 4 mm Hg decrease in IOP was seen at months 1, 2, 3[x2], 4, and 10. From these patterns, it appears that if medical cannabis use results in decreased IOP, the timing of that effect varies considerably.

Minnesota Department of Health
Office of Medical Cannabis
85 E 7th Place, Suite 220
PO Box 64882
St. Paul, MN 55164-0082
651-201-5598
health.cannabis@state.mn.us
www.health.state.mn.us

10/11/19

To obtain this information in a different format, call: 651-201-5598.

Benefits Reported on the Patient Self-Evaluation: Patients with First Enrollment July 2016-June 2017

Summary

Of patients included on the standard 8 symptom analysis (n = 5412), more than half experienced moderate to severe symptoms at baseline on all measures except for nausea (46%) and vomiting (20%). Of patients experiencing moderate to severe symptoms at baseline, anywhere between 32% and 68% achieved at least a 30% reduction in symptom severity (symptom improvement) within 4 months of their first medical cannabis purchase. The lowest proportion of patients reporting symptom improvements in the initial 4-month period were for pain (32%) and fatigue (45%) symptoms, while the greatest proportion of patients reporting symptom improvements were for vomiting (68%), nausea (61%), depression (60%), and lack of appetite (59%) symptoms. Similarly, a smaller proportion of patients were able to maintain those symptom improvements in the following 4-months for pain (40%) and fatigue (50%) symptoms compared to all other symptoms (maintained anywhere by 57%-69% of patients).

Benefits Reported on the Patient Self-Evaluation: Patients with First Enrollment July 2016-June 2017

The patient self-evaluation is required for patients to complete prior to each medical cannabis purchase. It includes questions to assess symptom severity, some of which are administered to all patients (standard set of 8 symptom measures) and some of which are tailored to symptoms for a given condition (condition-specific symptom measures). Since symptom data is collected prior to each patient's first medical cannabis purchase, symptom changes can be assessed over time and compared to baseline (baseline = patient responses to symptom questions just prior to their first medical cannabis purchase).

Standard 8 Symptom Measures

The standard 8 symptom measures that all patients receive are answered on a 0-10 numerical rating scale (NRS), with 0 indicating absence of the symptom to 10 indicating that the symptom is as bad as the patient can imagine (see Box 1). Therefore, higher scores on these measures indicate poorer management of these symptoms. Patients are asked to rate symptom severity over the past 24 hours.

Box 1. Listing of the Standard 8 symptom measures that all patients answer, including the response options available to patients.

Standard 8 Symptom Measures:

Anxiety; Lack of appetite; Depression; Disturbed Sleep; Fatigue; Nausea; Pain; Vomiting

Response Options (0-10 Numerical Rating Scale):

0 = Symptom not present;

10 = Symptom as bad as one can imagine

To understand whether patients derived any symptom benefits during their participation in the program, the following two questions were explored for each Standard 8 symptom measure:

QUESTION 1

Of those patients who experienced moderate to severe symptoms at baseline (score of 4 or higher at baseline), what percentage of them experienced at least a 30% improvement in symptoms within four months of their first medical cannabis purchase? The threshold of $\geq 30\%$ reduction on a 0-10 point scale was chosen because this threshold has been documented in clinical trials to represent clinically meaningful change – especially for pain reduction and spasticity reduction. Examples of $\geq 30\%$ change include moving from a score of 10 to a score of 7, from 9 to 6, from 8 to 5, from 7 to 4, etc.

QUESTION 2

If a patient achieved at least a 30% improvement on symptoms within 4 months of their first medical cannabis purchase (determined in Question 1), what percentage of them will, on average, still maintain that level of improvement in the four months following that initial 30% symptom improvement? [Four-month follow-up period]

To address Question 1 the following procedure was adopted for each standard 8 measure: all patients who scored 4 or higher at baseline were identified as those experiencing moderate to severe symptoms, and all standard 8 responses that were submitted within 4 months of their first medical cannabis purchase were retained. From this dataset, each patient's standard 8 responses were compared to their baseline response over time. The first instance a patient achieved at least a 30% symptom improvement was recorded, effectively demonstrating when – during the first 4 months following their first medical cannabis purchase – the patient achieved symptom improvement, if at all.

Calculating the percentage of patients who achieved $\geq 30\%$ symptom improvement within 4 months of their first medical cannabis purchase (Question 1) was done in two ways. In one method, the number of patients who achieved $\geq 30\%$ symptom improvement within 4 months

was divided by the total number of patients that ever made a first purchase (patients with baseline PSE data). In the other method, the number of patients achieving $\geq 30\%$ symptom improvement within 4 months was divided by patients who had submitted additional PSE data (beyond their baseline response) within 4 months of their first purchase. The denominator in the former method includes all patients who made a first purchase (all patients with a baseline PSE submission), while the latter method effectively restricts the denominator to those patients who submitted additional PSE symptom data following their baseline submission and within 4 months of their first purchase. Therefore, the former method allows for a more conservative estimation of symptom benefit. In the text of this report, we present results using the former, more conservative estimate of benefit. Those who made no additional purchases after their first purchase may have discontinued use because of lack of effectiveness, though they may have discontinued use for other reasons as well (i.e., medical cannabis cost, side effects, etc.).

Question 2 was addressed by observing all symptom responses in the four months following the time point when the patient first achieved $\geq 30\%$ symptom improvement. For each patient, all symptom responses identified during those follow-up four months were averaged together. Patients who, on average, still maintained at least a 30% symptom improvement from baseline were identified as those showing persistence in their symptom benefits.

Results on Standard 8 Symptom Measures

See Table 1 for results. The third column displays the percentage and number of patients (out of 5412 patients) experiencing moderate to severe symptoms at baseline (baseline response ≥ 4) on a given Standard 8 measure. Fourth column represents answer to Question 1: percentage (and number) of moderate to severe scorers at baseline who achieved at least a 30% symptom improvement at any time within 4 months of their first medical cannabis purchase. Fifth column shows the number of patients that had submitted symptom data during their designated 4-mo follow-up period (4 month time window that followed their initial symptom improvement). Symptom responses during this 4-mo time period were averaged together within each patient. The sixth column shows the percentage and number of patients who had achieved $\geq 30\%$ symptom improvement that had – on average – maintained at least that level of improvement in the 4-month follow-up period. Lastly, the seventh column shows the percentage of all patients who both achieved at least a 30% improvement in the first 4 months since their first medical cannabis purchase and maintained that improvement on average in the 4-month follow-up period.

Table 1. Overall Standard 8 Symptom Results (n = 5412).

All patients collapsed across conditions (n=5412)

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period following Initial ≥ 30% Symptom Improvement	d% of Patients Who Achieved ≥ 30% Symptom Improvement for at least 4 months(n)	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	75.5 (4085)	57.1 (2334)	1989	59.3 (1385)	33.9
Appetite Lack	54.3 (2937)	59.2 (1740)	1496	61.0 (1062)	36.2
Depression	64.9 (3511)	59.9 (2104)	1785	60.2 (1267)	36.1
Disturbed Sleep	88.6 (4793)	56.2 (2693)	2310	57.1 (1539)	32.1
Fatigue	92.8 (5020)	44.5 (2236)	1951	50.0 (1118)	22.3
Nausea	46.1 (2497)	60.9 (1520)	1298	62.7 (953)	38.2
Pain	95.8 (5185)	31.8 (1648)	1454	39.6 (652)	12.6
Vomiting	20.2 (1091)	68.0 (742)	617	69.3 (514)	47.1

Results on Standard 8 Symptom Measures Stratified by Qualifying Condition

Tables 2-11 below shows the responses to the standard 8 symptoms stratified by qualifying condition.

Table 2. Standard 8 Symptom Results in Patients with Intractable Pain (n = 4060).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	76.5 (3107)	58.2 (1809)	1563	58.6 (1060)	34.1
Appetite Lack	51.8 (2102)	62.2 (1307)	1140	61.6 (805)	38.3
Depression	66.2 (2689)	61.1 (1643)	1413	59.9 (984)	36.6
Disturbed Sleep	90.6 (3677)	57.3 (2107)	1831	56.5 (1190)	32.4
Fatigue	93.4 (3793)	45.7 (1735)	1531	49.8 (864)	22.8
Nausea	44.5 (1808)	64.3 (1163)	999	61.6 (716)	39.6
Pain	99.6 (4045)	29.4 (1188)	1076	35.8 (425)	10.5
Vomiting	18.5 (752)	71.8 (540)	454	70.0 (378)	50.3

Table 3. Standard 8 Symptom Results in Patients with Muscle Spasms (n = 736).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	77.7 (572)	61.2 (350)	293	56.6 (198)	34.6
Appetite Lack	53.4 (393)	65.9 (259)	224	61.4 (159)	40.5
Depression	63.9 (470)	63.8 (300)	256	60.3 (181)	38.5
Disturbed Sleep	89.9 (662)	56.0 (371)	321	56.3 (209)	31.6
Fatigue	92.0 (677)	47.0 (318)	275	51.3 (163)	24.1
Nausea	41.6 (306)	68.3 (209)	183	65.6 (137)	44.8
Pain	95.7 (704)	37.5 (264)	236	42.8 (113)	16.1
Vomiting	18.9 (139)	76.3 (106)	92	76.4 (81)	58.3

Table 4. Standard 8 Symptom Results in Patients with Cancer (n = 624).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	73.9 (461)	42.5 (196)	147	57.1 (112)	24.3
Appetite Lack	76.1 (475)	37.9 (180)	135	46.7 (84)	17.7
Depression	66.0 (412)	44.2 (182)	138	53.8 (98)	23.8
Disturbed Sleep	84.0 (524)	42.6 (223)	163	49.3 (110)	21.0
Fatigue	94.6 (590)	27.5 (162)	128	40.1 (65)	11.0
Nausea	63.0 (393)	37.7 (148)	112	52.7 (78)	19.8
Pain	89.9 (561)	30.7 (172)	127	40.1 (69)	12.3
Vomiting	32.9 (205)	46.3 (95)	69	58.9 (56)	27.3

Table 5. Standard 8 Symptom Results in Patients with Seizures (n = 207).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	75.4 (156)	67.3 (105)	91	62.9 (66)	42.3
Appetite Lack	49.8 (103)	71.8 (74)	64	67.6 (50)	48.5
Depression	59.9 (124)	75.0 (93)	79	66.7 (62)	50.0
Disturbed Sleep	76.8 (159)	67.3 (107)	90	58.9 (63)	39.6
Fatigue	87.0 (180)	62.2 (112)	98	51.8 (58)	32.2
Nausea	41.5 (86)	76.7 (66)	56	71.2 (47)	54.7
Pain	65.2 (135)	55.6 (75)	62	53.3 (40)	29.6
Vomiting	18.8 (39)	76.9 (30)	26	73.3 (22)	56.4

Table 6. Standard 8 Symptom Results in Patients with Inflammatory Bowel Disease, including Crohn's Disease (n = 185).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving $\geq 30\%$ Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial $\geq 30\%$ Symptom Improvement	% of Patients Who Achieved $\geq 30\%$ Symptom Improvement that Maintained it**	% of Patients that Both Achieved $\geq 30\%$ Symptom Improvement and Maintained It**
Anxiety	69.2 (128)	68.0 (87)	78	72.4 (63)	49.2
Appetite Lack	64.3 (119)	63.9 (76)	72	68.4 (52)	43.7
Depression	58.4 (108)	67.6 (73)	66	72.6 (53)	49.1
Disturbed Sleep	81.6 (151)	65.6 (99)	93	63.6 (63)	41.7
Fatigue	90.8 (168)	52.4 (88)	79	63.6 (56)	33.3
Nausea	68.6 (127)	67.7 (86)	81	69.8 (60)	47.2
Pain	89.7 (166)	54.8 (91)	84	58.2 (53)	31.9
Vomiting	32.4 (60)	83.3 (50)	47	76.0 (38)	63.3

Table 7. Standard 8 Symptom Results in Patients with Terminal Illness (n = 66).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	83.3 (55)	36.4 (20)	15	55.0 (11)	20.0
Appetite Lack	72.7 (48)	39.6 (19)	14	57.9 (11)	22.9
Depression	78.8 (52)	44.2 (23)	17	56.5 (13)	25.0
Disturbed Sleep	84.8 (56)	39.3 (22)	19	54.5 (12)	21.4
Fatigue	95.5 (63)	27.0 (17)	15	35.3 (6)	9.5
Nausea	53.0 (35)	45.7 (16)	14	68.8 (11)	31.4
Pain	93.9 (62)	22.6 (14)	10	28.6 (4)	6.5
Vomiting	24.2 (16)	43.8 (7)	6	71.4 (5)	31.3

Table 8. Standard 8 Symptom Results in Patients with HIV/AIDS (n = 42).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving $\geq 30\%$ Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial $\geq 30\%$ Symptom Improvement	% of Patients Who Achieved $\geq 30\%$ Symptom Improvement that Maintained it**	% of Patients that Both Achieved $\geq 30\%$ Symptom Improvement and Maintained It**
Anxiety	78.6 (33)	36.4 (12)	11	75.0 (9)	27.3
Appetite Lack	64.3 (27)	51.9 (14)	12	64.3 (9)	33.3
Depression	61.9 (26)	50.0 (13)	11	76.9 (10)	38.5
Disturbed Sleep	85.7 (36)	41.7 (15)	14	60.0 (9)	25.0
Fatigue	81.0 (34)	35.3 (12)	10	50.0 (6)	17.6
Nausea	57.1 (24)	50.0 (12)	11	66.7 (8)	33.3
Pain	81.0 (34)	32.4 (11)	9	36.4 (4)	11.8
Vomiting	19.0 (8)	50.0 (4)	3	75.0 (3)	37.5

Table 9. Standard 8 Symptom Results in Patients with Glaucoma (n = 40).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving $\geq 30\%$ Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial $\geq 30\%$ Symptom Improvement	% of Patients Who Achieved $\geq 30\%$ Symptom Improvement that Maintained it**	% of Patients that Both Achieved $\geq 30\%$ Symptom Improvement and Maintained It**
Anxiety	77.5 (31)	45.2 (14)	12	50.0 (7)	22.6
Appetite Lack	40.0 (16)	62.5 (10)	7	50.0 (5)	31.3
Depression	55.0 (22)	40.9 (9)	7	33.3 (3)	13.6
Disturbed Sleep	82.5 (33)	33.3 (11)	9	72.7 (8)	24.2
Fatigue	90.0 (36)	36.1 (13)	10	46.2 (6)	16.7
Nausea	35.0 (14)	57.1 (8)	6	62.5 (5)	35.7
Pain	82.5 (33)	45.5 (15)	13	40.0 (6)	18.2
Vomiting	22.5 (9)	66.7 (6)	5	83.3 (5)	55.6

Table 10. Standard 8 Symptom Results in Patients with Tourette Syndrome (n = 30).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	90.0 (27)	59.3 (16)	13	43.8 (7)	25.9
Appetite Lack	33.3 (10)	70.0 (7)	6	85.7 (6)	60.0
Depression	60.0 (18)	66.7 (12)	11	75.0 (9)	50.0
Disturbed Sleep	73.3 (22)	72.7 (16)	14	62.5 (10)	45.5
Fatigue	73.3 (22)	50.0 (11)	10	72.7 (8)	36.4
Nausea	16.7 (5)	80.0 (4)	3	50.0 (2)	40.0
Pain	53.3 (16)	62.5 (10)	9	50.0 (5)	31.3
Vomiting	6.7 (2)	50.0 (1)	1	100.0 (1)	50.0

Table 11. Standard 8 Symptom Results in Patients with ALS (n = 15).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving $\geq 30\%$ Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial $\geq 30\%$ Symptom Improvement	% of Patients Who Achieved $\geq 30\%$ Symptom Improvement that Maintained it**	% of Patients that Both Achieved $\geq 30\%$ Symptom Improvement and Maintained It**
Anxiety	53.3 (8)	50.0 (4)	3	50.0 (2)	25.0
Appetite Lack	40.0 (6)	50.0 (3)	2	33.3 (1)	16.7
Depression	66.7 (10)	40.0 (4)	3	50.0 (2)	20.0
Disturbed Sleep	66.7 (10)	40.0 (4)	4	75.0 (3)	30.0
Fatigue	86.7 (13)	23.1 (3)	3	33.3 (1)	7.7
Nausea	13.3 (2)	100.0 (2)	2	50.0 (1)	50.0
Pain	66.7 (10)	50.0 (5)	5	40.0 (2)	20.0
Vomiting	6.7 (1)	100.0 (1)	1	100.0 (1)	100.0

Condition-Specific Symptom Measures

Besides the Standard 8 measures which are administered to all patients, some patients received additional symptom questions on the PSE to more adequately address condition-specific symptoms. These include, among others, questions on seizure frequency for seizure patients, questions on spasm frequency for muscle spasm and ALS patients, and Crohn's activity in Crohn's patients. While patients received the same response options on the Standard 8 measures (respond from 1-10 on a numerical rating scale), response options for condition-specific measures varied as indicated in Table 12.

All condition-specific measures were investigated within the same framework as the Standard 8 measures: 1) what percentage of patients achieved symptom improvement within the four months since their first medical cannabis purchase compared to their baseline responses, and 2) what percentage of those achieving symptom improvement showed general persistence in the 4-month follow-up period. A summary of results are similarly presented in a table like those presented for the Standard 8 measures (see Table 12 below).

Table 12. Results on Symptom Improvements on Condition-Specific Measures.

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Condition	Condition-Specific Symptom Measure	# of Patients Included in Analysis	% of Patients Achieving Threshold Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial Threshold Symptom Improvement	% of Patients Who Achieved Threshold Symptom Improvement that Maintained it**	% of Patients that Both Achieved Threshold Symptom Improvement and Maintained it**
Intractable Pain	Composite PEG Measure	3982	44.1 (1755)	1540	49.0 (860)	21.6
	<i>Pain Intensity</i>	3977	36.6 (1455)	1279	45.3 (659)	16.6
	<i>Life Enjoyment Interference</i>	3962	49.7 (1968)	1719	50.6 (995)	25.1
	<i>General Activity Interference</i>	3951	50.0 (1976)	1713	51.3 (1013)	25.6
Muscle Spasms	Weekly Spasms Frequency	736	53.8 (396)	331	51.8 (205)	27.9
	0-10 Spasticity Scale	674	43.5 (293)	246	44.4 (130)	19.3
Cancer: Cachexia/Wasting	Weight	198	10.1 (20)	14	45.0 (9)	4.5
Seizures	Weekly Seizure Frequency	207	55.1 (114)	95	58.8 (67)	32.4

Table 12 Continued. Results on Symptom Improvements on Condition-Specific Measures.

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Condition	Condition-Specific Symptom Measure	# of Patients Included in Analysis	% of Patients Achieving Threshold Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial Symptom Improvement	% of Patients Who Achieved Threshold Symptom Improvement that Maintained it**	% of Patients that Both Achieved Threshold Symptom Improvement and Maintained it**
Inflammatory Bowel Disease, Including Crohn's Disease	Subset of HBI Measures Combined	185	62.7 (116)	103	56.0 (65)	35.1
	<i># Liquid Stools</i>	70	60.0 (42)	35	69.0 (29)	41.4
	<i>Abdominal Pain</i>	119	63.9 (76)	70	48.7 (37)	31.1
	<i>General Well-Being</i>	37	64.9 (24)	20	37.5 (9)	24.3
	Weight	185	14.1 (26)	24	53.8 (14)	7.6
Terminal Illness: Cachexia/Wasting	Weight	22	22.7 (5)	3	40.0 (2)	9.1
HIV/AIDS	Weight	42	19.0 (8)	5	50.0 (4)	9.5
Tourette Syndrome	Weekly Tic Frequency	30	43.3 (13)	9	46.2 (6)	20.0
ALS	Weekly Spasms Frequency	15	46.7 (7)	6	28.6 (2)	13.3
	0-10 Spasticity Scale	8	25.0 (2)	2	50.0 (1)	12.5

Glaucoma patients were also administered their own condition-specific measure, which was to report on the most recent intraocular pressure test (IOP) result and the date the test was administered on each patient self-evaluation. However, rather than analyzing for changes on the IOP test compared to a baseline IOP result, these results are presented below as reported by the patients (see Table 13). All IOP test results represented to the left of the “First Visit” column indicate results from tests occurring prior to the patient’s first medical cannabis purchase; everything to the right of that column are results occurring after the patient’s first purchase. Column names refer to month in which the test was reported to occur prior to or after first purchase. Note that these results are not directly coming from the practitioner who administered the IOP test – reliance on patient documentation and/or memory is a limitation in interpreting these results.

Table 13. Patient-Reported Intraocular Pressure Test Results from Glaucoma Patients (n = 40): Left Eye/Right Eye.

* before first medical cannabis purchase

** after first medical cannabis purchase

Patient	33- mo *	24- mo *	13- mo *	11- mo *	10- mo *	9- mo *	8- mo *	7- mo *	6- mo *	5- mo *	4- mo *	3- mo *	2- mo *	1- mo *	1- mo **	2- mo **	3- mo **	4- mo **	5- mo **	6- mo **	7- mo **	8- mo **	9- mo **	10- mo **	11- mo **	12- mo **
1					13 / 14							12 / 13														
2			19 / 18											19 / 18				15 / 15								
3														12 / 15			14 / 14	12 / 12								
4														16 / 16				14 / 14	14 / 14			14 / 13				
5														26 / 26												
6														10 / 12												
7														14 / 16												
8												25 / 25						16 / 16		16 / 14						

Table 13 Continued. Patient-Reported Intraocular Pressure Test Results from Glaucoma Patients (n = 40): Left Eye/Right Eye.

* before first medical cannabis purchase

** after first medical cannabis purchase

Patient	33- mo *	24- mo *	13- mo *	11- mo *	10- mo *	9- mo *	8- mo *	7- mo *	6- mo *	5- mo *	4- mo *	3- mo *	2- mo *	1- mo *	1- mo **	2- mo **	3- mo **	4- mo **	5- mo **	6- mo **	7- mo **	8- mo **	9- mo **	10- mo **	11- mo **	12- mo **	
9												26 / 29															
10					22 / 21															22 / 21							
11														1/ 1			8/ 10										
12														16 / 30	12 / 19		9/ 19										
13														19 / 18			14 / 16										
14														16 / 14													
15													25 / 25						24 / 25			21 / 21					
16														24 / 25		24 / 23	22 / 22	19 / 19								19 / 19	

Table 13 Continued. Patient-Reported Intraocular Pressure Test Results from Glaucoma Patients (n = 40): Left Eye/Right Eye.

* before first medical cannabis purchase

** after first medical cannabis purchase

Patient	33- mo *	24- mo*	13- mo *	11- mo *	10- mo *	9- mo *	8- mo *	7- mo *	6- mo *	5- mo *	4- mo *	3- mo *	2- mo *	1- mo *	1- mo **	2- mo **	3- mo **	4- mo **	5- mo **	6- mo **	7- mo **	8- mo **	9- mo **	10- mo **	11- mo **	12- mo **	
17												17 / 18	17 / 18														16 / 16
18														17 / 17		14 / 8											14 / 8
19		15 / 15													12 / 11			12 / 11									
20														20 / 21													
21													1 / 1		1 / 1	1 / 1				1 / 1							
22														12 / 12													
23											17 / 23			27 / 18												17 / 21	
24									21 / 16							18 / 15											15 / 18

Table 13 Continued. Patient-Reported Intraocular Pressure Test Results from Glaucoma Patients (n = 40): Left Eye/Right Eye.

* before first medical cannabis purchase

** after first medical cannabis purchase

Patient	33- mo *	24- mo *	13- mo *	11- mo *	10- mo *	9- mo *	8- mo *	7- mo *	6- mo *	5- mo *	4- mo *	3- mo *	2- mo *	1- mo *	1- mo **	2- mo **	3- mo **	4- mo **	5- mo **	6- mo **	7- mo **	8- mo **	9- mo **	10- mo **	11- mo **	12- mo **
25				18 / 18													19 / 20									
26														20 / 19												
27	20 / 24																		20 / 24							
28														39 / 39			15 / 14									
29														12 / 12		16 / 15										
30														25 / 25												
31												17 / 17					18 / 18		16 / 14	12 / 14	12 / 11	12 / 11	12 / 11	12 / 11	12 / 12	
32								28 / 26																		

Table 13 Continued. Patient-Reported Intraocular Pressure Test Results from Glaucoma Patients (n = 40): Left Eye/Right Eye.

* before first medical cannabis purchase

** after first medical cannabis purchase

Patient	33- mo *	24- mo *	13- mo *	11- mo *	10- mo *	9- mo *	8- mo *	7- mo *	6- mo *	5- mo *	4- mo *	3- mo *	2- mo *	1- mo *	1- mo **	2- mo **	3- mo **	4- mo **	5- mo **	6- mo **	7- mo **	8- mo **	9- mo **	10- mo **	11- mo **	12- mo **
33														17 / 19			15 / 16				15 / 16				24 / 22	
34											23 / 23					17 / 19				15 / 16				21 / 21		
35				22 / 24																						
36														21 / 21							20 / 20	20 / 20				
37														25 / 23	23 / 19						16 / 18					16 / 18
38														20 / 20	22 / 19		19 / 19		14 / 13			17 / 16	15 / 14		16 / 15	
39						18 / 25			15 / 18																	
40														15 / 15						18 / 18				20 / 20		

Caution is needed when interpreting the patient self-reported intra-ocular pressure results. It is possible that patients report incorrect values and dates of testing. Importantly, reported data provides little or no insight into changes in glaucoma therapies or other medications during the period after medical cannabis initiation. And, though we have record of which products are purchased when, without patient-level comparison of changes in product with changes in observed effect, we could miss differential impact of products. That analysis is beyond the scope of this report. With those caveats, we make the following summary observations.

After initiating medical cannabis use, fifteen of the 40 patients (38%) reported intraocular pressure measurements with a decrease in intraocular pressure (IOP) ≥ 4 mm Hg in at least one eye, 14 (35%) reported no follow-up results in the year after medical cannabis initiation, and 11 (28%) reported follow-up values with no decrease in IOP ≥ 4 mm Hg (three had IOP decrease = 3 mm Hg in one eye).

Among the 15 showing a decrease in IOP ≥ 4 mm Hg, 11 reported more than one measurement during the year after following medical cannabis initiation. Among these 11 with multiple reported measurements, the ≥ 4 mm Hg decrease in IOP was present in the first reported post-initiation result for six (at months 1[x3], 2[x2], and 3). In five patients, the ≥ 4 mm Hg decrease in IOP wasn't seen in initial reported result(s), but was present in a later result (at months 4, 5, 7, and 8 [x2]). Among the four with only one post-initiation reported result, the ≥ 4 mm Hg decrease in IOP was seen at months 3[x2], 4, and 10. From these patterns, it appears that if medical cannabis use results in decreased IOP, the timing of that effect varies considerably.

Minnesota Department of Health
Office of Medical Cannabis
85 E 7th Place, Suite 220
PO Box 64882
St. Paul, MN 55164-0082
651-201-5598
health.cannabis@state.mn.us
www.health.state.mn.us

10/11/19

To obtain this information in a different format, call: 651-201-5598.

Benefits Reported on the Patient Self-Evaluation: Patients with First Enrollment July 2015-June 2016

Summary

Of patients included on the standard 8 symptom analysis (n = 1512), more than half experienced moderate to severe symptoms at baseline on all measures except for vomiting (32%). Of patients experiencing moderate to severe symptoms at baseline, anywhere between 36% and 60% achieved at least a 30% reduction in symptom severity (symptom improvement) within 4 months of their first medical cannabis purchase. The lowest proportion of patients reporting symptom improvements in the initial 4-month period were for pain (36%) and fatigue (40%) symptoms, while the greatest proportion of patients reporting symptom improvements were for vomiting (60%), depression (57%), and nausea (56%) symptoms. Similarly, a smaller proportion of patients were able to maintain those symptom improvements in the following 4-months for pain (45%) and fatigue (49%) symptoms compared to all other symptoms (maintained anywhere by 52%-59% of patients).

Benefits Reported on the Patient Self-Evaluation: Patients with First Enrollment July 2015-June 2016

The patient self-evaluation is required for patients to complete prior to each medical cannabis purchase. It includes questions to assess symptom severity, some of which are administered to all patients (standard set of 8 symptom measures) and some of which are tailored to symptoms for a given condition (condition-specific symptom measures). Since symptom data is collected prior to each patient's first medical cannabis purchase, symptom changes can be assessed over time and compared to baseline (baseline = patient responses to symptom questions just prior to their first medical cannabis purchase).

Standard 8 Symptom Measures

The standard 8 symptom measures that all patients receive are answered on a 0-10 numerical rating scale (NRS), with 0 indicating absence of the symptom to 10 indicating that the symptom is as bad as the patient can imagine (see Box 1). Therefore, higher scores on these measures indicate poorer management of these symptoms. Patients are asked to rate symptom severity over the past 24 hours.

Box 1. Listing of the Standard 8 symptom measures that all patients answer, including the response options available to patients.

Standard 8 Symptom Measures:

Anxiety; Lack of appetite; Depression; Disturbed Sleep; Fatigue; Nausea; Pain; Vomiting

Response Options (0-10 Numerical Rating Scale):

0 = Symptom not present;

10 = Symptom as bad as one can imagine

To understand whether patients derived any symptom benefits during their participation in the program, the following two questions were explored for each Standard 8 symptom measure:

QUESTION 1

Of those patients who experienced moderate to severe symptoms at baseline (score of 4 or higher at baseline), what percentage of them experienced at least a 30% improvement in symptoms within four months of their first medical cannabis purchase? The threshold of $\geq 30\%$ reduction on a 0-10 point scale was chosen because this threshold has been documented in clinical trials to represent clinically meaningful change – especially for pain reduction and spasticity reduction. Examples of $\geq 30\%$ change include moving from a score of 10 to a score of 7, from 9 to 6, from 8 to 5, from 7 to 4, etc.

QUESTION 2

If a patient achieved at least a 30% improvement on symptoms within 4 months of their first medical cannabis purchase (determined in Question 1), what percentage of them will, on average, still maintain that level of improvement in the four months following that initial 30% symptom improvement? [Four-month follow-up period]

Results on Standard 8 Symptom Measures

See Table 1 for results. The third column displays the percentage and number of patients (out of 1,512 patients) experiencing moderate to severe symptoms at baseline (baseline response ≥ 4) on a given Standard 8 measure. Fourth column represents answer to Question 1: percentage (and number) of moderate to severe scorers at baseline who achieved at least a 30% symptom improvement at any time within 4 months of their first medical cannabis purchase. Fifth column shows the number of patients that had submitted symptom data during their designated 4-mo follow-up period (4 month time window that followed their initial symptom improvement). Symptom responses during this 4-mo time period were averaged together within each patient. The sixth column shows the percentage and number of patients who had achieved $\geq 30\%$

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symptom improvement that had – on average – maintained at least that level of improvement in the 4-month follow-up period. Lastly, the seventh column shows the percentage of all patients who both achieved at least a 30% improvement in the first 4 months since their first medical cannabis purchase and maintained that improvement on average in the 4-month follow-up period.

Table 1. Overall Standard 8 Symptom Results (n = 1512).

All patients collapsed across conditions (n=1512)

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	# of Patients Reporting at Moderate to Severe Symptoms at Baseline	% of Patients Reporting at Moderate to Severe Symptoms at Baseline	% of Patients Achieving $\geq 30\%$ Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial $\geq 30\%$ Symptom Improvement	% of Patients Who Achieved $\geq 30\%$ Symptom Improvement that Maintained it**	% of Patients that Both Achieved $\geq 30\%$ Symptom Improvement and Maintained It**
Anxiety	1185	78.4	53.8 (638)	460	53.1 (339)	28.6
Appetite Lack	963	63.7	53.7 (517)	383	57.1 (295)	30.6
Depression	1000	66.1	56.8 (568)	419	56.7 (322)	32.2
Disturbed Sleep	1323	87.5	50.3 (665)	519	52.0 (346)	26.2
Fatigue	1381	91.3	40.2 (555)	415	48.6 (270)	19.6
Nausea	864	57.1	55.6 (480)	362	59.2 (284)	32.9
Pain	1312	86.8	36.3 (476)	329	45.0 (214)	16.3
Vomiting	480	31.7	60.2 (289)	213	57.8 (167)	34.8

Results on Standard 8 Symptom Measures Stratified by Qualifying Condition

Tables 2-10 below shows the responses to the standard 8 symptoms stratified by qualifying condition.

Table 2. Standard 8 Symptom Results in Patients with Muscle Spasms (n = 667).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	82.9 (553)	54.8 (303)	250	60.7 (184)	33.3
Appetite Lack	61.0 (407)	58.2 (237)	198	65.0 (154)	37.8
Depression	70.6 (471)	58.0 (273)	227	63.0 (172)	36.5
Disturbed Sleep	90.6 (604)	49.7 (300)	265	61.7 (185)	30.6
Fatigue	93.6 (624)	42.0 (262)	227	55.3 (145)	23.2
Nausea	54.9 (366)	63.1 (231)	195	65.4 (151)	41.3
Pain	96.0 (640)	33.8 (216)	188	51.4 (111)	17.3
Vomiting	28.8 (192)	65.1 (125)	103	66.4 (83)	43.2

Table 3. Standard 8 Symptom Results in Patients with Cancer (n = 405).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving $\geq 30\%$ Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial $\geq 30\%$ Symptom Improvement	% of Patients Who Achieved $\geq 30\%$ Symptom Improvement that Maintained it**	% of Patients that Both Achieved $\geq 30\%$ Symptom Improvement and Maintained It**
Anxiety	76.3 (309)	45.0 (139)	112	56.1 (78)	25.2
Appetite Lack	79.3 (321)	39.3 (126)	102	57.1 (72)	22.4
Depression	67.7 (274)	48.5 (133)	101	55.6 (74)	27.0
Disturbed Sleep	87.7 (355)	42.0 (149)	122	47.0 (70)	19.7
Fatigue	94.8 (384)	25.3 (97)	83	41.2 (40)	10.4
Nausea	69.9 (283)	38.2 (108)	85	60.2 (65)	23.0
Pain	87.9 (356)	28.9 (103)	80	40.8 (42)	11.8
Vomiting	41.5 (168)	47.6 (80)	64	57.5 (46)	27.4

Table 4. Standard 8 Symptom Results in Patients with Seizures (n = 299).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving $\geq 30\%$ Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial $\geq 30\%$ Symptom Improvement	% of Patients Who Achieved $\geq 30\%$ Symptom Improvement that Maintained it**	% of Patients that Both Achieved $\geq 30\%$ Symptom Improvement and Maintained It**
Anxiety	67.6 (202)	67.3 (136)	120	71.3 (97)	48.0
Appetite Lack	48.5 (145)	76.6 (111)	97	73.9 (82)	56.6
Depression	52.8 (158)	73.4 (116)	101	74.1 (86)	54.4
Disturbed Sleep	80.9 (242)	69.0 (167)	155	63.5 (106)	43.8
Fatigue	82.3 (246)	61.8 (152)	143	64.5 (98)	39.8
Nausea	46.2 (138)	72.5 (100)	93	79.0 (79)	57.2
Pain	63.5 (190)	60.0 (114)	106	69.3 (79)	41.6
Vomiting	30.1 (90)	80.0 (72)	66	79.2 (57)	63.3

Table 5. Standard 8 Symptom Results in Patients with Crohn's Disease (n = 102).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	85.3 (87)	57.5 (50)	43	54.0 (27)	31.0
Appetite Lack	78.4 (80)	53.8 (43)	37	58.1 (25)	31.3
Depression	66.7 (68)	51.5 (35)	31	65.7 (23)	33.8
Disturbed Sleep	87.3 (89)	42.7 (38)	37	65.8 (25)	28.1
Fatigue	94.1 (96)	36.5 (35)	31	48.6 (17)	17.7
Nausea	70.6 (72)	65.3 (47)	31	59.6 (28)	38.9
Pain	95.1 (97)	41.2 (40)	32	47.5 (19)	19.6
Vomiting	30.4 (31)	54.8 (17)	16	82.4 (14)	45.2

Table 6. Standard 8 Symptom Results in Patients with Terminal Illness (n = 81).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	74.1 (60)	51.7 (31)	28	58.1 (18)	30.0
Appetite Lack	79.0 (64)	37.5 (24)	19	45.8 (11)	17.2
Depression	66.7 (54)	48.1 (26)	22	61.5 (16)	29.6
Disturbed Sleep	80.2 (65)	44.6 (29)	28	55.2 (16)	24.6
Fatigue	93.8 (76)	21.1 (16)	14	37.5 (6)	7.9
Nausea	69.1 (56)	44.6 (25)	23	64.0 (16)	28.6
Pain	88.9 (72)	19.4 (14)	11	50.0 (7)	9.7
Vomiting	43.2 (35)	57.1 (20)	18	50.0 (10)	28.6

Table 7. Standard 8 Symptom Results in Patients with HIV/AIDS (n = 48).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving $\geq 30\%$ Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial $\geq 30\%$ Symptom Improvement	% of Patients Who Achieved $\geq 30\%$ Symptom Improvement that Maintained it**	% of Patients that Both Achieved $\geq 30\%$ Symptom Improvement and Maintained It**
Anxiety	91.7 (44)	50.0 (22)	20	68.2 (15)	34.1
Appetite Lack	81.3 (39)	48.7 (19)	17	63.2 (12)	30.8
Depression	70.8 (34)	47.1 (16)	15	75.0 (12)	35.3
Disturbed Sleep	91.7 (44)	50.0 (22)	18	50.0 (11)	25.0
Fatigue	85.4 (41)	46.3 (19)	15	47.4 (9)	22.0
Nausea	68.8 (33)	60.6 (20)	17	65.0 (13)	39.4
Pain	93.8 (45)	40.0 (18)	14	50.0 (9)	20.0
Vomiting	41.7 (20)	50.0 (10)	9	80.0 (8)	40.0

Table 8. Standard 8 Symptom Results in Patients with Tourette Syndrome (n = 28).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving $\geq 30\%$ Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial $\geq 30\%$ Symptom Improvement	% of Patients Who Achieved $\geq 30\%$ Symptom Improvement that Maintained it**	% of Patients that Both Achieved $\geq 30\%$ Symptom Improvement and Maintained It**
Anxiety	92.9 (26)	69.2 (18)	17	72.2 (13)	50.0
Appetite Lack	28.6 (8)	50.0 (4)	3	75.0 (3)	37.5
Depression	71.4 (20)	75.0 (15)	14	86.7 (13)	65.0
Disturbed Sleep	75.0 (21)	76.2 (16)	16	75.0 (12)	57.1
Fatigue	75.0 (21)	66.7 (14)	13	50.0 (7)	33.3
Nausea	17.9 (5)	100.0 (5)	5	80.0 (4)	80.0
Pain	60.7 (17)	64.7 (11)	11	90.9 (10)	58.8
Vomiting	3.6 (1)	100.0 (1)	1	100.0 (1)	100.0

Table 9. Standard 8 Symptom Results in Patients with Glaucoma (n = 21).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving $\geq 30\%$ Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial $\geq 30\%$ Symptom Improvement	% of Patients Who Achieved $\geq 30\%$ Symptom Improvement that Maintained it**	% of Patients that Both Achieved $\geq 30\%$ Symptom Improvement and Maintained It**
Anxiety	66.7 (14)	42.9 (6)	6	50.0 (3)	21.4
Appetite Lack	33.3 (7)	85.7 (6)	5	66.7 (4)	57.1
Depression	66.7 (14)	85.7 (12)	11	58.3 (7)	50.0
Disturbed Sleep	85.7 (18)	61.1 (11)	10	54.5 (6)	33.3
Fatigue	90.5 (19)	42.1 (8)	7	37.5 (3)	15.8
Nausea	28.6 (6)	16.7 (1)	1	100.0 (1)	16.7
Pain	85.7 (18)	33.3 (6)	6	50.0 (3)	16.7
Vomiting	4.8 (1)	0.0 (0)	0	-- (0)	0.0

Table 10. Standard 8 Symptom Results in Patients with ALS (n = 21).

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Standard 8 Symptom Measure	% of Patients Reporting at Moderate to Severe Symptoms at Baseline (n)	% of Patients Achieving ≥ 30% Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial ≥ 30% Symptom Improvement	% of Patients Who Achieved ≥ 30% Symptom Improvement that Maintained it**	% of Patients that Both Achieved ≥ 30% Symptom Improvement and Maintained It**
Anxiety	81.0 (17)	52.9 (9)	7	55.6 (5)	29.4
Appetite Lack	38.1 (8)	87.5 (7)	5	57.1 (4)	50.0
Depression	71.4 (15)	40.0 (6)	5	50.0 (3)	20.0
Disturbed Sleep	85.7 (18)	33.3 (6)	6	83.3 (5)	27.8
Fatigue	95.2 (20)	35.0 (7)	7	71.4 (5)	25.0
Nausea	42.9 (9)	55.6 (5)	4	80.0 (4)	44.4
Pain	81.0 (17)	47.1 (8)	7	25.2	11.8
Vomiting	9.5 (2)	50.0 (1)	1	100.0 (1)	50.0

Condition-Specific Symptom Measures

Besides the Standard 8 measures which are administered to all patients, some patients received additional symptom questions on the PSE to more adequately address condition-specific symptoms. These include, among others, questions on seizure frequency for seizure patients, questions on spasm frequency for muscle spasm and ALS patients, and Crohn's activity in Crohn's patients. While patients received the same response options on the Standard 8 measures (respond from 1-10 on a numerical rating scale), response options for condition-specific measures varied as indicated in Table 11.

All condition-specific measures were investigated within the same framework as the Standard 8 measures: 1) what percentage of patients achieved symptom improvement within the four months since their first medical cannabis purchase compared to their baseline responses, and 2) what percentage of those achieving symptom improvement showed general persistence in the 4-month follow-up period. A summary of results are similarly presented in a table like those presented for the Standard 8 measures (see Table 11 below).

Table 11. Results on Symptom Improvements on Condition-Specific Measures.

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Condition	Condition-Specific Symptom Measure	# of Patients Included in Analysis	% of Patients Achieving Threshold Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial Threshold Symptom Improvement	% of Patients Who Achieved Threshold Symptom Improvement that Maintained it**	% of Patients that Both Achieved Threshold Symptom Improvement and Maintained it**
Muscle Spasms	Weekly Spasms Frequency	629	48.0 (302)	225	57.6 (174)	27.6
	0-10 Spasticity Scale	618	36.4 (225)	197	47.1 (106)	17.2
Cancer: Cachexia/Wasting	Weight	147	13.6 (20)	15	45.0 (9)	6.1
Seizures	Weekly Seizure Frequency	262	68.3 (179)	150	70.9 (127)	48.5
Crohn's Disease	Subset of HBI Measures Combined	102	51.0 (52)	41	42.3 (22)	21.6
	# Liquid Stools	41	51.2 (21)	17	57.1 (12)	29.3
	Abdominal Pain	73	53.4 (39)	29	35.9 (14)	19.2
	General Well-Being	15	46.7 (7)	5	28.6 (2)	13.3
	Weight	102	20.6 (21)	18	57.1 (12)	11.8
Terminal Illness: Cachexia/Wasting	Weight	29	20.7 (6)	5	50.0 (3)	10.3

Table 11 Continued. Results on Symptom Improvements on Condition-Specific Measures.

*within 4 months of First Purchase (n)

**for at least 4 months (n)

Condition	Condition-Specific Symptom Measure	# of Patients Included in Analysis	% of Patients Achieving Threshold Symptom Improvement*	# of Patients with Data in 4-mo Period Following Initial Threshold Symptom Improvement	% of Patients Who Achieved Threshold Symptom Improvement that Maintained it**	% of Patients that Both Achieved Threshold Symptom Improvement and Maintained it**
HIV/AIDS	Weight	48	14.6 (7)	3	42.9 (3)	6.3
Tourette Syndrome	Weekly Tic Frequency	48	60.7 (17)	15	76.5 (13)	46.4
ALS	Weekly Spasms Frequency	18	33.3 (6)	4	66.7 (4)	22.2
	0-10 Spasticity Scale	15	20.0 (3)	3	100.0 (3)	20.0

Glaucoma patients were also administered their own condition-specific measure, which was to report on the most recent intraocular pressure test (IOP) result and the date the test was administered on each patient self-evaluation. However, rather than analyzing for changes on the IOP test compared to a baseline IOP result, these results are presented below as reported by the patients (see Table 12). All IOP test results represented to the left of the “First Visit” column indicate results from tests occurring prior to the patient’s first medical cannabis purchase; everything to the right of that column are results occurring after the patient’s first purchase. Column names refer to month in which the test was reported to occur prior to or after first purchase. Note that these results are not directly coming from the practitioner who administered the IOP test – reliance on patient documentation and/or memory is a limitation in interpreting these results.

Table 12 Continued. Patient-Reported Intraocular Pressure Test Results from Glaucoma Patients (n = 21): Left Eye/Right Eye.

* before first medical cannabis purchase

** after first medical cannabis purchase

Patient	11- mo*	5- mo*	4- mo*	3- mo*	2- mo*	1- mo*	1- mo**	2- mo**	3- mo**	4- mo**	5- mo**	6- mo**	7- mo**	9- mo**	10- mo**	11- mo**	13- mo**
12						12 / 10			12 / 12								
13						22 / 14	22 / 14										
14						9 / 26		8 / 12									
15					17 / 18		19 / 24										
16	22 / 20						16 / 16		17 / 17	16 / 16						18 / 19	
17						23 / 23	16 / 16	19 / 25		16 / 19	16 / 19			16 / 18			
18				10 / 12				12 / 15									
19						30 / 22		19 / 16		26 / 16							
20					17 / 19	19 / 17	19 / 17										
21						17 / 26	17 / 28		20 / 25				19 / 20				24 / 28

Caution is needed when interpreting the patient self-reported intra-ocular pressure results. It is possible that patients report incorrect values and dates of testing. Importantly, reported data provides little or no insight into changes in glaucoma therapies or other medications during the period after medical cannabis initiation. And, though we have record of which products are purchased when, without patient-level comparison of changes in product with changes in observed effect, we could miss differential impact of products. That analysis is beyond the scope of this report. With those caveats, we make the following summary observations.

After initiating medical cannabis use, eight of the 21 patients (38%) reported intraocular pressure measurements with a decrease in intraocular pressure (IOP) ≥ 4 mm Hg in at least one eye, 4 (19%) reported no follow-up results in the year after medical cannabis initiation, and 9 (43%) reported follow-up values with no decrease in IOP ≥ 4 mm Hg.

Among the 8 showing a decrease in IOP ≥ 4 mm Hg, 6 reported more than one measurement during the year after following medical cannabis initiation. Among these 6 with multiple reported measurements, the ≥ 4 mm Hg decrease in IOP was present in the first reported post-initiation result for five (at months 1[x3], 2, and 4). In one patient, the ≥ 4 mm Hg decrease in IOP wasn't seen in the initial reported result, but was present in a later result (at month 9). Among the two with only one post-initiation reported result, the ≥ 4 mm Hg decrease in IOP was seen at months 1 and 2. From these patterns, it appears that if medical cannabis use results in decreased IOP, that effect usually occurs within the first few months but can vary.

Minnesota Department of Health
Office of Medical Cannabis
85 E 7th Place, Suite 220
PO Box 64882
St. Paul, MN 55164-0082
651-201-5598
health.cannabis@state.mn.us
www.health.state.mn.us

10/11/19

To obtain this information in a different format, call: 651-201-5598.

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Appendix A: Patient-Reported Benefits from Surveys

Note: Word choice and spellings have been retained as written by respondent to avoid inadvertent mischaracterization of intent. Brackets have been used to explain words redacted to prevent individual identification or for other reasons. Benefits are broken down by qualifying condition and by benefit score rating.

Severe and Persistent Muscle Spasms

1: No Benefit

- no benefits
- none yet

2

- Did not help control my son's seizures but we at least never seen any negativeside effects of the medication
- Don't recognize sublingual drops
Helps relaxing
- Improved sleep
- physical movement
- The "Patient Discontinuation Survey" didn't have a place to comment when choosing "won't buy again", so I want to be sure someone got this. What I get from the medical market in other states works much better for pain relief and spasm reduction, in both flower and concentrate. I think it's because the critically important terpenes (more important than THC/CBD) are removed in the processing at [MANUFACTURER] and not added back, like they are in other places. Without better processing (more expensive) or giving patients access to flower (least expensive), MN's processing is removing nearly all of what makes cannabis a medicine - terpenes.

3

- Less overall pain
- Mood may have been better slightly. Still not good, but better.
- More confidence in public
- Less tremors
- no nausea, It helped with spasms
- reduced pain and spasm
- Reduced tremors slightly

4

- upper spinal relief
- 1. Pain reduction
- 2. Sleep
 - Being able to buy my medicine legally and not being considered a criminal from law enforcement for using a plant as medicine!

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- Better sleep
- Better sleep some nights, some days I am able to be more active and I have a viable option for pain relieve.
- Calming my anxiety, sleeping a full night, waking feeling well rested
- Decrease in spasticity and pain.
- Has controlled arthritis and fibromyalgia.
- Helping relieve my muscle spasms
- I get more sleep.
- I am feeling better.
- It has reduced my muscle spasms, and is helping with nerve pain, and seems to have reduced the number of migraines I get.
- Less nausea
- Less symptoms
- Moderate relief from muscle spasms/cramps
- My spasticity has improved some with the medical cannabis, but I still experience at least three or four times a week, severe pain, cramping and spasticity in myhamstrings.
- nausea / pain / spasims
- nausea is slowing down.
- Nerve pain. I can actually ride in a car again without crying.
- pain relief
- Pain relief
- Reduction in pain.
- Relaxation which reduces nerve pain
- Relaxing of muscles in legs - better walking distance, less pain, more active
- Remediation of muscle spasm symptoms
- Rest
- Sleep better.
- spasticity reduction
- Spouse and PT think I am less stiff

5

- one benefit of taking medical cannabis for my condition symptoms is the effectiveness how it ease the pain of my spasticity.
- better appetite, less nausea less pain less anxiety
- Better sleep
Less anxious
Very little need for vicodin
- Better sleep, less spasms, less spasticity
- cears
- decrease in auras, muscle spasms and pain.
- decreased muscle spasms and pain, decreased abdominal discomfort, better mood, less anxiety

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- Eliminating muscle spasms, relaxed muscles, relief of pain, increased improvement of sleep
- Helps my sleep
- I can Manage my pain and muscle spasms to keep the pain at a tolerable level.
- I don't feel much pain, and not as severe as it always was before.
- I hope to greatly reduce the persistent pain in my lower extremities from my toes to mid thighs.
- I no longer get, AT ALL almost, or greatly reduced on the small occasion that I do, migraines and/or small seizures. (And there are so many other benefits!!)
- I use it for sleep and at the beginning of the day always. It has been very helpful in me getting restful sleep and also helpful in having help with pain relief during the day without the awful side effects of opioids (excessive drowsiness and constipation)
- improved nausea
- improved anxiety
- spasms- only a little better
- Improved nausea, improved appetite, less pain, less spasms, relaxed spasms.
- Increased help with muscle spasms and inflammation in lower back. Also lower back chronic pain.
- Increased sleep time - was between 2 - 3 hours a day, now 3 - 4 hours a day. Pain from knee nerve damage has been lowered to very manageable now.
- It has decreased my spasms, lessens some pain, and helps me sleep better.
- It has improved things a little, but because of the cost, not sure it's worth it.
- It has reduced my numbness and spasms
- knowing that it's legal and I don't have to worry about anything
- lack of chronic pain. Lack of twitches.
- Less aching in my joints and less all over body pain.
It has also helped my anxiety.
- Less pain and discomfort.
- Less spasms
- limits my muscle spasms
- little less depressed.
- lowered my pain so I could be up more during day , helped with anxiety from having pain for so long as well
- muscle spasm pain was greatly reduced.
- Muscles relax a great deal so I am in less pain so I can sleep and move around easier.
- My most important benefit has been discovering that my severe pain can be modified with the use of medical cannabis.
- Pain management
- Appetite
- pain reduction
- pain relief
- Pain relief and relaxation.

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- pain relief, muscle relaxer
- Relaxation of Muscle spasms...
- Relief of muscle spasms
- Relieves pressure.
Engages senses
Allows for easier sleep
- Restful and relaxed sleep.
- Sleep
- Slowed my spasms.
- The back spasms are better.
- Vape seemed to help the pain. Liquid not so much.

6

- The same dose each and every time consistent delivery
- A large reduction in symptoms, allowing me to participate in my daily life without a large number of limits my symptoms would place on me - stools decreased from over 8 a day to about 2 with much less blood and mucous in stools. Pain has reduced to a tolerable amount.
- Able to eat. In less pain. Don't need my depression meds any more.
- Almost immediate pain relief from vaping and help settling my leg spasms.
- An increase in appetite, and decrease of muscle spasms
- Appetite
- Calms the restless leg down quite a bit
- Decrease in severity of spasms
Decrease in duration of spasms
Notable decrease in pain
More so than other pain med and anti spasmotic meds
- decreased intensity of muscle spasms
- dramatic decline in seizures
- Elder of symptoms
- Fewer spasms and less pain when standing and less pain when walking
- First I have to say I replaced a decade of narcotics with only medical cannabis with no relapse. I had a failed back surgery and severe sciatic pain and back pain daily. I also suffer from a rare blood disorder called Acute Porphyria's. its nearly impossible to treat however i have found some relief in that as well with this medication. I found the products still to be weak compared to other staes. Also the selection is so very limited. Not to mention the price is three time higher then industrystandard.
I have had great improvements in pain, which has also allowed me to be much more active with my family. My muscle spasms although are still there I find most days the medication helps considerably, however my issues are serious and sometimes nothing helps at times. I also suffer from severe anxiety attacks and have seen less of those as well. over all not only myself but my family sees positive change and I feel healthier, happier and feel currently this is making a huge positive impact on my life.

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- Freedom from pain in the evenings and sleep
- Has allowed me to move forward in life
- Have slept better than I have in 14 years! Due to not worrying all night if I was going to have a seizure in the morning
- helps calm the spasms in my eye lids due to blepharospasm
- Helps to lower stress, my muscle spasms have been pretty much nulled! My stomach issues having been like before, cramps have been minimized, just feel quite a bit better!
- Helps with anxiety (better mood). Back, did help some! The pain is still there, caused of disks and ceribre needs operated on the back. But I do like the vapor medicalcannabis
- helps with leg spasms greatly.
- I am having less falling and in addition I have had a reduction in my OxyContin from three 40 MG tablets per day to three 20 MG tablets per day. That is half.
- I experience very little nausea when taking the medicine
- I have been able to cut out the pain pills and am down to one muscle relaxer per day. I am not as tired as much. I can't believe how much better I feel
- I have been able to delay needing shots for my blephrospasm
- I have been able to get a good nights rest using the [HIGH THC] pill. I have also gained clarity and energy from taking 1 [HIGH CBD PRODUCT] 2 times daily.
- I'm less in pain
I don't have spasm in my back and legs that much.
I'm less moody
- It calms the spasms and the vapor gives relief right away.
- It has decreased the pain level and increased stamina to exercise
- It has helped with my bladder issues and leg weakness greatly.
- It helps my spasms and helps me to "not pay attention" to the pain as much.
- It helps with pain the most then it helps with my muscle spasms and helps me sleep at night do to the burning of my legs
- legal access to medication
- Less pain and calmer
- Less pain, easier sleep
- less sharp back pain
- Less spasms and nausea.
- less stiffness in the muscles, joints, bones
- lessening spasms and muscle pain
- loosens muscles
- Medical cannabis is one of only a few treatments to help control symptoms of my neurological disorder
- Might save my life
- More comfortable and not as much guarding position of shoulders.
- more urinary control
- Muscle spasm/ pain reduction

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- My spasm's are less frequent, pain I have in my back is tolerable, relaxes me.
- My stomach (core) feels more normal (calm) and my bowel movements are less often - have more form - not as much liquid & gas.
- nausea control
- Nausea has improved
- Appetite
- no spasms at all
- Overall decrease in pain sensitivity
- Pain
- PAIN CONTROL
- pain management
- Pain reducton
- More mobility
- Pain relief
- Pain relief is the biggest benefit. Also less cramping.
- pain relief
- anxiety relief
- Pain relief,
- Peace of mind.

Worry is like PTSD. I only make arrangements I can back out of in case I have a flare. Anticipation of a new flare is always on my mind. I don't know how long a flare is going to last or how bad it will be. In the middle of a flare, I didn't have any form of relief so I'd panic because of severity of symptoms and no treatment.

Now, I still have MS PTSD because I've had problems for so long, but I know I have >something< that will help the problem. Though a flare may last a while, I know I'll be able to break through the mental barrier of panic because I have a treatment that works. It's very comforting after years of only suffering.

- Reduced pain. Able to eat. And spasm are less
- reduces muscle spasms
- Reducing tone and spasticity
- reduction in pain and muscle spasms as well as at least a 50% reduction of monthly use of prescription pain medications.
- Reduction of pain due to muscle spasms and less side effects compared to other medications
- Relaxes my muscles
- Relief from painful spasticity
- relieve anxiety
- sleep better
- Relieve the pain of Charlie horses in my legs. Tremors from MS less noticeable.
- Relieves pain, helps me relax, helps me sleep. I feel more comfortable and have more energy.
- Rigidity is so much better!

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- sleeping
- Sleeping/spasms
- Spasm relief and that leads ultimately to pain management.
- spasms decreased
sleep improved greatly
pain relief
less Xanax and opiates used
- Stopped my seizures, convulsions and shaking .
- The pain I feel in my lower half of my body cease to exist while taking medical marijuana. With that being said, it's difficult to take it during my work hours, because it makes me feel less attentive So, I'm between a rock and a hard place. NO pain or pain.
- The Spasms are less frequent as they were before.
- Using Medical Cannabis PRN for anxiety & irritability has replaced the need for PRN Ativan use completely.

7: Great Deal of Benefit

- Very few side effects, actually feel a lot better getting off the narcotics, Vicodin, methadone, and Valium . Did not have an appetite and did not want to leave the house before, I feel so much better it's like a miracle
- 1. Spasm and pain reduction.
2. I have stopped all pain meds and off two spasm meds. This is amazing for me. I've been on the spasm meds for over 10 years, now, when I feel tightness or a spasm starting, I take a small amount of high CBD cannabis and the spasm does not develop. It's been a life saver for me.
- 1. Being able to take my medicine legally, avoiding problems being evicted for use of cannabis.
2. Assistance with nausea
3. Help with muscle spasms - I have been able to work out in Physical therapy more intensely than before helping to reduce pain.
4. Reduction of narcotic pain medication.
- 1. Helps control Back Pain and Muscle Spasms without narcotic fears.
2. Relaxing and Sleep
3. Appetite
- 1. large decrease in pain
2. large decrease in back spasms
3. my depression isn't as bad
4. my panic-anxiety attacks have decreased and I am not anxious all the time
5. my foot drop is 95% better
6. I have been able to decrease my pill medications by FIVE!
- Ability to relax with decreased pain
- Able to stop taking all pain meds and stay off. Helps all of my symptoms to be better. Unfortunately too expensive to buy what I need to stay off pain pills and have better

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

quality of life. Need plant form, then medicine will cost less and last longer. I do not like smoking, vaping oils into my body.

If mn law had followed other states and not been stupid about this law people could get certified properly with insurance, and have access to Affordable medical cannabis. Instead many, many people are not benefiting or using program because of all the hoops you have put into place.

In 2016 I should be able to google doctors that are certifying for medical cannabis and make sure they take my insurance. Instead I had to take almost a year to find a clinic that certifies and takes insurance.

The way it is now is better than nothing at all but the way it is now is like dangling a bone for your dog that he just can't ever get a full bite of.

- Access to a good consistent medication that helps multiple problems.
- After 29 years I no longer have migraine headaches everyday.
- Almost all muscle spasms and pain associated with spasms are gone. I used to have constant nerve triggered pain that is minimal now. Results were almost immediate. I am sleeping way better now also.
- Although there is no proof that I directly benefited, I took a large dose of the oral suspension and was able to enjoy the holidays like a normal person for the first time in a long while. Pain hasn't returned as long as I continue to medicate with medicinal grade Cannabis.
- anti inflammatory
- Appetite stimulation
- Back seizures gone
arthritis gone
- Being able to cope with my daily pain, and reducing the amount of other medications I am prescribed is very important to me.
- being able to sleep without waking up in spasm
- Being able to treat my epilepsy with cannabis oil and not having to worry about breaking the law. I have been seizure free ever since I began using cannabis oil.
- Besides helping with my back issues, my general pain and soreness have been less, as well. Also, helps me just be in a better mood and think a little more clearly.
- Better quality of life, greatly reduced pain, greatly reduced spasms and exacerbations, less stiffness able to sleep through the night.
- Better sleep, appetite, pain reduction and sense of well being.
- Calming of my muscles n joints from spasms
Also helping with food intake
- calming of my spasms
- calmness
- calms my inner nerves & muscle pain & bad spasms & hand tremors & sleep
- Cannabis has helped my Crohn's in nearly every way. There's no way I can choose just one benefit that's the most important to me. The highlights of my experience have

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

been; no more abdominal pain, a 15 weight gain(I was underweight beforehand) and a reduction in my inflammation.

Thanks to cannabis crohns no longer controls my life.

- Cannabis has helped with keeping the chrons calm. I made it through the holidays with no flare ups.
- Clearer head since I have been using this program instead of pain pills.
- comfort, pain relief, hope.
- Cured my nonstop UTI
- Decrease in muscle spasms and increase in appetite with a reduction in my discomfort and pain.
- Don't have to take as many pain pills
- Ease of pain and consequently tension and the ability to be more active.
- Even though I have increased in number of muscle spasms each day due to my MS, when I take my meds both the pain and the spasms subside for a number of hours. My physical therapy sessions are more beneficial as well because I can actually bend my legs easier.
- Far less muscle spasms. A little less pain associated with muscle spasms.
- fewer muscle spasms in my neck. less pain than before I started the program.
- freedom to be excepted and relieve from mussel spasams
- Functionality. I am able to withstand more hours with out pain and muscle spasms. They are still there, but greatly reduced.
- Geneal improvement in quality of life
- Getting off all my narcotic pain medications, no more muscle relaxers, or sleeping pills.
- getting off pain meds
- Going from disabled to working again.. Having my life back. Being able to leave my house again.
- got ripped off for 450 dollars at [MANUFACTURER], they lied to me before i made my purchase, the oil was not consistant - hardly effective, bad consulting they should be shut down along with their grower. [MANUFACTURER] was ok, better quality, can't afford the prices i am poor and in pain.
- Greater mobility and less inflammation.
- Helped reduce swelling in my ankle a great deal, among other benefits
- helps reduce the pain associated with spasticity in me legs,
- Helps with my issues...
- I am able to sleep at night.
- I am in significantly less pain. I can function throughout the day so much better than I could before the cannabis program. It is like night and day.
I have less dizziness from vertigo with the cannabis
I have better mobility of my neck
- I am not on any narcotic pain meds anymore, and I am not having to reposition myself every 15 to 30 min, and am sleeping for longer periods at night.

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- I am registered under the condition of Tourette's Syndrome. I used to experience a great deal of muscle spasms and tics. Since starting the program I have had many comments from friends and family saying that they have hardly noticed any tics in the previous few months.
- I could walk better.
- I feel less stress resulting in fewer muscle spasms. I can sleep sometimes at night without using the Ambien which I have needed for over 15yrs. It allows me to have a better perspective of any given situation because I am not feeling stressed out or as if I were a criminal. I have been able to discontinue my opioid pain medicine that I took for over four years after my accident. I can remain calm in many situations that used to upset me emotionally. I can enjoy my grandchildren and family so much more now that both physical and emotion health are improved with medical cannabis.
- I have a great deal of relief from my muscle spasms. I get the relief without the anxiety I experience from cannabis I get off the street. I believe the medications work better than the stuff on the street.
- I have been able to manage my chronic migraine headaches much better. I have been able to decrease my use of abortive medications.
- I have been able to reduce my Parkinson's meds by about 70%. I sleep much better. I am less depressed.
- I have less pain in my body & less migraines
- I have periods of the day where i experience little to no pain.
- I have stopped taking two narcotic pain and one skeletal muscle relaxer RX's. And the VERY painful spasms are much more tolerable.
- I take less or smaller doses of other prescription meds.
I sleep better at night with less pain.
I move more freely
- I was quickly able to get off both Valium and Ambien Both were heavy duty drugs that I was dependent on, not because I wanted to take them, but had to. I was so glad to get off them and feel somewhat normal.
- I'm not kicking my wife while I'm asleep. The leg is still restless but not as bad as before. And I don't have as much pressure/dullness in the back of my neck/head area.
- Increased muscle coordination
Increased attentiveness
Increased cognitive function
Increased mobility
Increased positive moods
Decreased spasm severity
Decreased seizures
- It controls my mind grains and headaches caused by my condition.
- It has allowed me to reduce the number of medications I take; both type and quantity.
- It has caused a marked decrease in my essential tremor, severe muscle spasms in my osteoporosis ridden degenerative disc disease. Lower degree of pain and less in

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

frequency. I also have severe GI IBS and pancreatic issues, involving tumors that cause painful abdominal muscle spasms. The two pancreatic tumors are inoperable, and I need to have them scanned annually for any sign of malignancy. I also feel it helps a patient's attitude and sense of hope. I know that's not a medical concern, but it's a great side effect, "Hope"!!! Thank You!!!

- It has cut down my back spasms at least 50% or more and since I've been on medical program for Minnesota I haven't fallen over once which team is a great deal
- It has evened out my muscle spasms and made things both possible and more comfortable. It has slowed down the Dystonia storms.
- It has helped my sleep thru the night and a lot less spasms
- It has made my quality of life better to make it short and sweet
- It has reduced my muscle spasms by 90%. It helps me sleep at night. For example, it helps control my spasms so they don't wake up and I have less pain. The amazing thing it's also a nerve blocker like Neurontin or gabapentin. Here's another amazing fact. It helps control my autonomic dysreflexia. Out of every benefit this has undoubtedly given me my quality of life back. At night, if you understand autonomic dysreflexia, my blood pressure would shoot up to 150 or 180 before bedtime. This is dangerous as my normal range is 80 or 90 over something. My muscle spasms at night shoot my blood pressure up. I felt like I was going to have a stroke and could have if they are not controlled. My head would pound like it was going to explode with a severe headache, my face becomes extremely hot and flushed, my hands and fingers become numb (weird side effect), my heart starts to pound against my chest as it has to work harder to pump blood. So heart rate goes down as blood pressure goes up. It's helped the inflammation of my joints because they ache less. There is not "one" benefit in my case but many. All of them are important to my quality of life. I finally feel like I have that back now!!!
- It has replaced all opioid medications and allows me to function and participate in family and social activities again.
- It helps with my spasms to be less as well as not as painful
- It reduces the number of attacks and severity of the leg cramps at night.
- It relaxes my muscles in my body to help lower pain and allowing me to keep the narcotic medication down to the bare minimum. Without the program I would be unable to stay functioning because the narcotics make me tired and worn out and want to do nothing. With the use of Medical Marijuana and keeping the Narcotics down allows me to keep my day to a functioning day no matter how slow I may be, but I am not worn out because I can use the vaporizers to help the muscles so much. That in return makes me feel that my life is somewhat productive instead of dormant.
- It works on too many levels. I can eat better and I usually get nausea and it works great for that. My arthritis is much better. I am still dealing with the side effects of radiation my cancer Dr. says. I guess with no stomach and most intestines gone I don't usually eat as well or feel good (healthy) enough to even get up and go to my office.

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- I can afford to but have added the stock market to my ways to make additional money. I can puff and some days with in hours I may go to the office.
 - it works quickly to relieve muscle spasms,,helps control pain during physical work, controls pain to a certain extent,helps give you opportunity to quality of life.
 - [PATIENT]'s mobility has increased.
 - some pain relief
 - Less lower back pain, increased apatite.
 - Less muscle aches and better sleep.
 - Less muscle spasm's = body not being as fatigued allowing me to perform my physical therapy better.
 - Less muscle spasms!!
 - less mussel spasms and pain
 - less nerv pain
 - Less pain and inflammation in legs and ankles. Didn't feel so wore out at the end of the day. Was able to relax and sit for long periods with less stiffness and joint pain. Overall I had less pain
 - Less Pain
 - Less sleep issues
 - More hunger'
 - Less mood swings
 - All around better feeling of life
 - less petit mal seizures , better sleep at night and , reduced muscle spasms
 - less seizures
 - Less spasms helps me relax.
 - Many fewer spasms. I went from several per hour every day to several per day. Much improvement! I also have less anxiety. My confidence has increased from feeling more relaxed.
 - Much less pain, in my bowel and neurapathy pain. I can tell almost immediately if I forget to take the medication. Within one or two hours, the pain in the gut/bowel area is back. I never realized how terrible I have felt until after I started to feel better. I have had bowel pain as long as I can remember (pre-school) and I thought everyone felt like that. It is all I ever knew and it was getting worse each year.
 - much less weakness/pain
 - easier sleeping
 - not as many spasms in the morning
 - Muscle spasms stopped completely. I was able to walk much better and sleep better at night.
 - Muscle spasms, burning, pain, level of thing's would be a couple less for sure, but depending on affordability, and the level of it like I was doing great making real strides, I lost like a lot of weight and my body sores from other medicine went away a lot on my skin by using the cannibas, and I just had a fall recently that just is not normal but happens, an set me way back again now so or my numbers are effected cuz that just

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

happened... Takes time especially nerve pain, when a feather hurt's a nerve just a touch, and scar tissue rapping on them hurt's alot as it did me again now among other thing's! But the medicine help's me in my ailment struggles.

- My horrible chronic spasms have greatly diminished.
- My insomnia is so much better,my muscle spasms have calmed down some,I have an appetite now,my muscle pain has lowered quite a bit to the point I can get somethings down around the house,I was walking with a cane but I am no longer at this point...I believe my balance over all is better at this moment in time.
- My muscle spasms are getting easier to cope with on a daily basis
- My muscle spasms have decreased and my nausea and general pain decreased
- My muscles were spasm all day long , what this medicine is doing is helping them to relax more , at first I was scared because the spasms were so tight around my bone , when it relaxed more the bone started to hurt and pulse ate . After that went I new what was happening . I keep at a steady pace and the muscles are reacting good to it . I am so grateful for this medicine , and can't believe I was on the opposite side of this medicine . It truly is like a miracle !!!!
- My severe spasms of my neck, spine, legs, feet, arms, and hands become very mild, and almost absent when medicated with Cannabis treatment!
- Nausea, pain in my back
- No crohns disease flare ups since starting treatment
- No longer need Botox to control spasms in thighs
- No more street weed
- no spazims and sleeping well
- Off topic from my qualifying condition, my root disease is Mast Cell Disease that stemmed from Childhood Leukemia. I have always had a low WBC, and now I am in the normal WBC range, with my WBC having DOUBLED!!! Since the start of using MC regularly from [MANUFACTURER]. I use the 50/50 THC-CBD ratio. THIS IS A HUGE IMPACT and I am nothing that my Mast Cell Disease is becoming more calm, which is leading to less pain, reactions, inflammation and muscle spasms.
- One of the benefits that I did get it from medical cannabis is the ability to get up and walk take a shower take a drive and have an ability to cope with extreme muscle spasm and back pain daily and work with these problems and medical cannabis help me deal with all that not just a bunch of painkillers and other medications that I can't spell medical cannabis help me through my injury.
- Only usage of the oil helped! But it's much too expensive.
- Pain & Muscle Spasms
- Pain control
- pain control and relaxing of muscle spasms while allowing me to be coherent and continue to work.
- Pain goes away
- Pain is more manageable

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

Anxiety is way down (PTSD)

- pain relief
- Pain relief
- pain relief
- sleep completely through the night
not as moody because im in pain
- pain relief and nausea relief
- Pain relief has been a major benefit as I am able to control pain from my backspasms very well with medical cannabis. Not having to take opiods is great!!
- Pain relief nausea relief
- Pain relief, increased mood/motivation, less time in bed, more time enjoying life not focused on pain
- Pain relief.
- pain spasms
- Reduced pain and anxiety
- Reduced pain from muscle spasms, reduced headaches.
- Reduced seizures and spasms feel more normal on cannabis.
- Reduction in spasms
- reduction in spasms
reduction in pain
reduction in ""jibberish"" due to pain and spasms
better sleep
less anxiety
reduction of harmful pharmaceutical medications (side affects)
- reduction of interocular eye pressure; also reduction in muscle cramps and chronic pain
- Reduction of spasms
- Reduction or outright elimination of my intractable pain.
- Relaxation
- Relaxes me at the end of the day . Makes my pain go away.
- Relaxes me I don't have as many tremers and the pain is better than before.
- Relief from muscle spasms
- Relief from my syptoms
- Relief of muscle spasms with no side effects
- relief of severe pain
- RELIEF using an all natural method ... Cannabis is a holistic formula of balancing your condition and very-very little side effects compared to the Rx monopoly. If it works, keep in simple, keep it green. ㄟㄟㄟ
- Relieves muscle spasms
- Seizures are less intense
- Send starting medical cannabis my quality of life has increased dramatically. My my pain has subsided almost completely my energy level has taken a 360 turn for the better. I am a young woman and my late mid thirties and I would wake up every day feeling like I

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

was 90 years old. I would spend most my days in bed with no energy and the pain kept me from venturing out and enjoying my young children. Medical cannabis has also stimulated my appetite as well as help my anxiety and depression. I previously self medicating the street marijuana and even knowing the price difference and the cheaper I am able to get it from the streets I will never go back. I am also a cigarette smoker and the medical cannabis has reduced money smoking regular cigarettes in which in turn has increased my lung capacity and constant bronchitis feeling. My family and friends have seen a difference in me and the way I live my day-to-day life. Instead of denying the activities but I want to enjoy it I know have the ability to live my life the way I want to.

- Significantly decreased the pain/cramping in my lower legs and feet
- sleep, calmness
- Sleep well. Reduces pain
- Sleeping has improved! Mental health has improved! Pain control is optimal
- spasm control
- spasm relief
- spasm/pain lessened, reduced
- SPASMS AND NECK PAIN
- Starting to be able to slowly cut out other medications, noticing that I'm feeling healthier from the cannabis cause that's all natural and I haven't had as many attacks and when an attack does one on ice noticed just a couple of hits and the attack is under control.
- the ability to control my pain management without the groggy feeling I get when I use pain medication.
- the ability to move around more without having spasms and pain
- The ability to stop or drastically decrease my lower back spasms at any point in the day.
- The cancer-fighting effects from the cannabis oil.
- The medical cannabis has given me much more flexibility and an increased range of motion in my movement..
- The most important benefit to me is that this program has got my life moving again!! I cannot believe the favorite things I can now do thanks to the Minnesota Medical Cannabis Program, also the new things I can try, and still stay comfortable. Because of this program, I am getting so much time away from my Facio Scapulo Humeral Muscular Dystrophy, used to take away from me!! I can do more to care for myself, my home, my dog, my husband. I can get out and about, I can eat better, there are just so many benefits from this program I do NOT want to give back!
- the pain relief and it helps sleep
- The pain relief is great and my spasms are less and less
- The reduced muscle spasms in my legs has made it possible to take more steps than I thought would be possible again.
- The relief from pain
The feeling of well being

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- the Vape oil allows me to go to work without vomiting. also the pills help with inflammation and pain
- This is typed by his spouse. [PATIENT] has a TBI (traumatic brain injury). He says that it has had a major beneficial effect on his quality of life. One of the unexpected side effects has been a clarity of thought. He use to get confused doing some small tasks and some how it helps him to think clearer. He has been exceedingly more motivated and accomplishing more.
- This treatment has significantly reduced the frequency and intensity of cervical muscle spasms and the associated severe headaches.
- To be able to do things that I haven't been able to do for years because of pain and immobility.
- Vomiting control, tremor relief, ability to eat, went off antidepressants, can sleep.
- walking better
- We have seen a girl go from not interacting, to interacting. No appetite to appetite. Balance also seems better.
- When I use medication I can move. Without it I am in too much pain to move or engage with the world.
- Within 1 week of use, my tics disappeared and have stayed gone even with occasional use. This has never happened previously in my life, so it is very effective.
- Yes, It benefits me every day and my quality of life has greatly improved as a result, for the first time in my life i am neither under or over medicated.
- Reduced spasticity, reduced pain, improved Sleep, improved depression and anxiety.

Cancer

1: No Benefit

- Didn't like it and didn't use it
- None

2

- Increase appetite
- Some relaxation
- the first thing I discovered was the importance of taking time. second thing was taking things for granted!

4

- Appetite
- dull pain, sleep
- eating more,
- Facilitated my sleep
- helped with the nausea
- helps with pain
- Helps with sleep. Helps with pain.

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- I am feeling better.
- learning
- relaxation in the midst of pain, better appetite, some alleviation of pain.
- Relief from pain
- relief of stress
pain relief
- This survey was sent to [PATIENT], who died on [DATE].

5

- better sleep, less pain and fatigue, not as anxious, continued to have a appetite.
- [PATIENT] is dead. But it kept his potential nausea very low and help with any potential pain.
- Evening pain is eased with Cannabis before bed.
- Helping w/ pain management, sleep, reducing nausea
- It helped with my nausea.
- Keeping my appetite up and removing nausea symptoms.
- Little benefit to my cancer pain but a surprising improvement of at least 75% in my chronic arthritis pain.
- loosened up
- One benefit was it helped with my nausea and vomiting but not as well as I would have hoped. I had to puff on the vape pen consistantly to relieve me of the nauseated feeling instead of the 1 to 2 puff recommended dose.
- Pain
- Pain and nausea control
- pain management
- Pain relief
- Seems to have helped the neuropathy symptoms and also gives me an all over sense of well being - also helps with the nausea symptoms after chemotreatments.
- Seems to slow down pain rolls and eye strain.
- Sleep aid

6

- ability to eat
- An increase in appetite, and decrease of muscle spasms
- appetite enhancement
- Appetite, more relaxed
- Appetite
- Decrease in pain and imflammation
- help with pain
- I'm comfortable and able to eat and sleep
- Improved appetite, somewhat less pain
- improved pain load mood and sleep
- It has helped manage pain and anxiety.

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- leg cramps and nausea
- Less jabbing pain in feet from Neuropathy - better sleep
- less narcotic pain medicine
much better pain control
fewer breakout pain incidences
- Less pain, calmer about the situation
- Less spasms and nausea.
- Might save my life
- My stomach (core) feels more normal (calm) and my bowel movements are less often -
have more form - not as much liquid & gas.
- nausea control
- Not feeling the pain in bones/muscles and good feelings for a terminal illness
- Pain control
- Pain Management
- pain reduction, better sleep, increased appetite
- pain relief and help with sleep
- Really helps with pain from cancer treatments as well as resulting anxiety from multiple
surgeries and permanent scars, etc.
- Reduction of Nausea and pain, and increase in appetite.
- reduction of side effects or neg. effective of other forms of treatment I have been on.
- relieve anxiety
sleep better
- Sleep and being able to eat, and reduced nausea
- Spasm relief and that leads ultimately to pain management.
- Stomach cramps gone
Anxiety relief
Nausea relief
Sleep

7: Great Deal of Benefit

- Because of the THC, I feel like getting up and doing things. Prior to having the cannabis, I
just laid on the couch. I felt like I was just waiting to die. 2. I do not use the percocet. I
do not want to have to take pain pills. Period. To many people are getting addicted to
these things. 3. I do not get the dry mouth or canker soars since I hardly use the anti
nausea drugs.
- Ability to create appetite and relieve pain
- ABLE TO EAT AND MAINTAIN MY WEIGHT PLUS MY NAUSEA HAS DECREASE
TREMENDOUSLY .
- able to eat food. helps keep nausea down.
- Appetite, was losing weight fast! Didn't have one! Now got it back! And gained 20
pounds! From this.
- Appetite. During chemo weeks I can barely eat and the THC helps a lot.
- Being able to start weaning myself from opiates I've been on for ten years.

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- controlling nausea
- Controlling nausea
- Coping with nausea, being able to eat and maintain weight
- [PATIENT] has passed away. I am her daughter and was her care giver. She was open to trying medical cannabis and we got the liquid form. It was a saving grace. She was in a lot of pain and when prescribed medications did NOT work - we started this and it kept her calm and relaxed. I am very thankful that we were able to have this option available. It helped to make her last months more bearable and truly it would have been miserable without it.
- Eating
- general overall feeling of well-being...pain relief
- Getting appetite back, and attitude adjustment.
- Greater mobility and less inflammation.
- Help with sleeping
- Helped ease pain. Calmness and appetite. Have no appetite on chemo without it
- helped with nausea
- I am able to sleep pain free for 7 to 8 hours a night
- I have not had issues with nausea at night and my PSA counts are going down.
- I used cannabis to treat my constant nausea during chemotherapy. This option seemed to be a very effective option after I was unable to take pills orally. Later on during treatment I used the medical cannabis to see for myself how it would treat the pain I was in. I wouldn't say medical cannabis a great painkiller, however the cannabis seemed to break my focus on the pain better than the oxycodone alone. I really feel that my quality of life was better using the cannabis.
- I was able to discontinue the use of multiple dangerous drugs.
- I was able to get off all my anti nausea medication which allowed me to
Get off all the anti constipation medication. Prior to being in the cannabis program I had no appetite and had lost 35 lbs I have been able to put back on 15 lbs. My quality of life after chemotherapy treatments turned around substantial. An added bonus was the pain relief from a chronic back pain, it has helped significantly with my pain management.
- Improved quality of sleep.
- Increased appetite and motivation.
- Instead of sleeping all day [PATIENT] was social and wanting to be with family and friends.
- It helps a lot with my pain level. Since I started this program I have not needed to increase my opioid medication to control my pain. I many times use the vaporizer in place of oxycodone for breakthrough pain. When my anxiety is very hi I use the vaporizer. It has made a very positive difference in my quality of life at this point.
- less bowel urgency, less pain, less anxiety
- Makes me eat/ help me sleep relax pain is not as bad

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- Medical cannabis has almost completely relieved my pain and nausea associated with my cancer and the effects of treating my cancer with chemo (I have chemo every three weeks for the rest of my life due to metastatic colon cancer).
- Mitigation of nausea and sleeping assistance.
- My inflammation from chemo and radiation completely went away! My pain and suffering has really decreased because of this oil it is a miracle!!!
- my nausea after chemo is gone in less than a minute after one inhalation from my vaporizer
- nausea control makes me hungry with my condition helps with the lulls in life
- Nausea and Pain
- Pain and sleeping
- Pain control while still allowing me to live. I can not handle opiates.
- Pain control
 - Appetite
 - Anxiety reduction
- Pain reduced: 70% - 80%,
 - Better sleep
- pain relief
- Pain relief
- Pain relief
- Pain relief
 - Sleep
 - Nausea
- reduced vomiting.
- Reduction in pain, muscle tension, and anxiety. Sleep has also improved.
- Relaxing, peaceful sleep and wake up relaxed... less anxiety..
- relief from Nausea, gave me appetite
- Relief of breakthrough pain
- Relief of nausea
 - increased appetite
 - relief of anxiety
 - better sleep
- Relief of pain
 - Ability to Sleep
 - Restoration of Appetite
 - Gaining of strength
 - Increased Mobility
 - Restoration of concentration
- Relief of the nausea that I have all day with the chemo drug I am on.
- Relieves anxiety and nausea
- Relieves anxiety, depression and pain and is a natural solution as opposed to a man made pill.

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- since I've started using the oil my brain cancer has maintained its size, it isn't getting any bigger and it isn't getting any smaller.
- Sleep aid. Anxiety decrease.
- The cancer-fighting effects from the cannabis oil.
- the cannabis takes away the upset stomach feeling instantly. it also is a great sleep aid. it helps me with my apatite and takes away the pain. and i don't have to worry about addiction.
- With my cancer diagnoses and treatment, I've found relief while taking the cannabis!!! I get relief from pain, relief from nausea, relief from insomnia.
- Without the medical cannabis I am not able to eat at all. With the cannabis I have been able to maintain a healthy weight and get the nutrition I need during my treatment.
- I died

Seizures

1: No Benefit

- At first thought seemed to be more aware but not we are off it he is still more aware
- None - lives in a group home and group home can not store or administer or risk lose fed. funding
- Nothing really
- Other health issues occurred and I stopped the cannabis before the dose was at a high enough level to do anything. So we are not a fair representation of effectiveness of cannabis for seizure control

2

- "possible" slight decrease in seizure activity
- Being able to legally get marijuana in MN.
- I believe it has reduced seizures. It's difficult to fully know without my epilepsy dr. not involved.
I've tried approximately 13 different seizure medications over the past decade, non of which has helped a great deal.
I'm trying to follow the process that the Dr. used for other medication.
Take a small amount look for side effects and or change to the seizures.
If side effects try to lower the amount.
If no side effects try to find an amount that works.
I'm trying to do this on my own but a Dr. is needed.
It's not clear if it's working or not, so keep that in mind when looking at my answers to the questions.
- I was experiencing relief from stress and anxiety the first two months but I am no longer
- more present cognitively
-Also, being able to try it and stop wondering if it was going to help.
- slight seizure reduction, but too many side effects

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

▪ Speech Development

3

- Decrease the amount of seizures and seizure meds
- fewer seizures
- knowing we have had the option to try medical cannabis when other treatments have failed
- [PATIENT] was having clonic seizures. All muscle tone would leave body and she would drop. She no longer has those seizures
- More aware of my surroundings; thinking more clearly.
- Reduction of seizures

4

- A slight decrease in seizures, though still not enough control. Also, improved cognitive skills.
- Breathing thru seizures more?
- comfort, has a tethered spine seems to feel less irritability.
- Cognitive thinking. More alert.
- Helps with diaphragmatic flutters
- I have less seizures
- It may have lessened seizure activity.
- Less muscle twitching and sleeping better..
- less seizure activity
- lessening of pain
- Limiting seizures
- Local
- My daughter is the patient and I have seen more cognitive improvements on CBD oil.
- seeing [PATIENT]'s seizures reduce overall.
- seizure reduction
- Seizures respond quicker to emergency med
- Thinks clearer talks more

5

- Anxiety/Depression
- Calmed my muscles and seemed to help my seizure
Also helped me sleep all night, not waking up 5-6 times a night
- tears
- Controlling his seizures as well as I'm probing cognitive functioning!
- decrease in auras, muscle spasms and pain.
- decrease in seizures
- decreased seizures

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- Developmental Growth: Using hands more, fine and gross motor skill improvement within the first couple weeks! More verbal, smiles more, babbles and talks more, reaches for toys more, overall has enhanced his quality of life in a very short time.
- Fewer seizures, more cognitively aware/focused/alert, improved sleep
- He seems so much happier since we've switched to the [HIGH CBD PRODUCT].
- I know for a fact that this med is helping me
- Less aching in my joints and less all over body pain.
It has also helped my anxiety.
- Less Seizures (Four patient reports)
- less seizures, more mental clarity, overall improved wellness
- limits my muscle spasms
- Medical cannabis has been amazing for my son. No harmful side effects or lifelong medical problems from taking it. Such as Risperdal, ect. I would however remove the MCT from all cannabis products. It is not a good thing for people with stomach or neurological issues. Which is usually why a person would need this or desire relief from dealing with these issues. MCT is for people with none of those problems.
- Mood
- More alert or aware
- My daughter went for the full month of September with NO seizures when she first started on cannabis. October and November were not so good. This past month we tried a different formula to see if we can get better control. Still more adjustments are needed.
- Pain and seizure relief. Finally off oxycodone after 1.5 years
- reduction in seizures with no side effects and no mood problems
- reduction of seizures
- Reduction of seizures.
- [PATIENT]'s spasms and twitching have significantly decreased
- Seizures are more under control even when other med levels are low.
- The first 2 days, very sleepy. After that the first week, her small seizures were gone, the second week her mobility increased and her verbal language increased. 3rd week, she got her cycle, so everything went out the window with that. 4th week she got a cold. We had dosage changes but did not see the 2 week awesome things again.
- [PATIENT] more alert and vocal than ever before

6

- Better cognition and less seizures
- Decrease in seizures overall, especially tonic-clonic seizures, & few rescue meds.
- Decreased seizure activity
- dramatic decline in seizures
- Feel better. More energy.
- Fewer seizures
- fewer startle seizures

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- Have slept better than I have in 14 years! Due to not worrying all night if I was going to have a seizure in the morning
- Helps eliminate or reduce certain side effects from the other epileptic medication.
- [PATIENT] began babbling and made new sounds! His synapses seemed to be firing faster.
- Increased alertness, increased development, less seizures,
- Large decrease seizures. Caregivers have not had to rescue him since beginning medication.
- Less convulsions, dizziness, auras, confusion during everyday moments which are signs of possibly losing consciousness, or are very problematic to function at work.
- Less seizures
- less seizures,
- managing pain
- Marked reduction in frequency of seizures, their duration and severity
- My postictal state after a seizure went from 4-5 days down to 1-2 days.
- Reduced seizures (Two patient reports)
- Reduction of number of intractable seizures plus reduction of length of seizures and a quicker recovery time from seizures.
- Reduction of seizures quality and quantity
- responsiveness. core strength.
- Sara is much more alert and cognitively connected in her conversation.
- Less severe seizures
- Seizure control
- Seizure reduction was the main goal, and we have seen seizure reduction. In addition, [PATIENT] has a better quality of life. We are taking him off all other pharmaceuticals. He is eating better, sleeping better and is a happier child.
- Seizures are weaker and less
- seizures have decreased
- Seizures have decreased in amount and intensity.
- seizures have reduced in frequency and there are no negative side-effects to the medication
- Stopped my seizures, convulsions and shaking .
- The seizures are stopping and the dizziness is going away. [PATIENT] is more controllable and is able to control himself better as well. He's still autistic 😊

7: Great Deal of Benefit

- 75% reduction in seizures
- 95% reduction in uncontrolled seizures
- 98% seizure reduction, elimination of persistent headaches, and we were able to wean 75% of child's benzodiazepines, meaning that her Quality of Life has significantly improved, as have all of her abilities.

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- Being able to treat my epilepsy with cannabis oil and not having to worry about breaking the law. I have been seizure free ever since I began using cannabis oil.
- Better cognition
 - Better focus
 - Less anxiety
 - Better mood
- Better sleeping, less muscle cramping, less periods of seizure-like activity.
- Control of seizures, FINALLY!!! :) = Quality of life for my little boy!!!
- Decreased # of seizures.
- [PATIENT] is still on anti seizure meds, but he has not had any seizures from forgetting to take them (Keppra) on several occasions...normally he would have.
- [PATIENT] has been seizure free since Sept 21, 2015!!!
- Epilepsy, helping me stay seizure free, and also helps anxiety, calm down
- Fewer Seizures Better Calmer Communicating Ability
- Grand mal seizure free
 - Sleep duration has dramatically increased
 - Better quality of life (only one side effect compared to the horrendous side effects from the pharmaceutical medications he was on)
- Having no more seizures is the biggest reason.
- his ability to come off some of his other meds and be more "present", calm, and content.
- I am in significantly less pain. I can function throughout the day so much better than I could before the cannabis program. It is like night and day.
 - I have less dizziness from vertigo with the cannabis
 - I have better mobility of my neck
- I am not having any seizures at all
- I feel more alive, less depressed, outgoing, functional, pain relief from my headaches and eye twitches, also just overall life has improved since this has come available to me.
- I started out on a normal dose of antiseizure meds and was still experiencing seizures that lasted over 3 minutes in duration. I then increased my antiseizure meds to the maximum recommended dose however I still was having seizures lasting over 3 minutes. I had my last seizure 4 days after starting the cbd cannabis medicine. It lasted less than 1 minute. I can happily say that I am over 4 months seizure free.
- Increased focus, ability to calm self more easily, able to be present in the moment, engaging more with others, better sleep, increased verbalization. (averaging 5-10 words each day, prior to CBD oil >3) better digestion
- Increased muscle coordination
 - Increased attentiveness
 - Increased cognitive function
 - Increased mobility
 - Increased positive moods
 - Decreased spasm severity

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

Decreased seizures

- It has greatly helped with the seizures and quality of life has improved very much. The quality of life has improved so much that much more is possible than was not before, such as community outings without extreme behavior outbursts.
- I've only had a seizure when I increased the cannabis and that's normal. Otherwise, I haven't had any seizures randomly in my sleep or out running since I've started the cannabis.
- Less frequency of seizures. 20/day to 2-5/day
- less headaches less anxiety
- less petit mal seizures, better sleep at night and, reduced muscle spasms
- less seizures
- less seizures
- More alert. Less myoclonic seizures.
- More seizure control and more energy
- My daughter has had an over 95% reduction in seizures and gotten off many harmful medicines since starting the Medical Cannabis program.
- No grand mal seizures
- No seizures since beginning treatment. Sleep is continuous and more restful.
- No seizures since I started taking the [HIGH CBD] Medical Marijuana formula!!!! It's amazing!!! :-)
- One month without seizures!!!
- Only usage of the oil helped! But it's much too expensive.
- Pain reduction and now able to sleep 6-7 hours per night vs 2 before using medicinal marijuana.
- Pain relief has been a major benefit as I am able to control pain from my back spasms very well with medical cannabis. Not having to take opioids is great!!
- Quality of life
- QUALITY OF LIFE & WAY LESS SEIZURES!!!!!! 90% LESS!!!!!!!!!!!!!!
- Reduced seizure activity & sense of "neurological calm" on good days; also mental clarity and sharpness
- Reduced seizure frequency, anxiety reduced, less partial seizures, mood booster
- reduction in seizure frequency for my son
- reduction in seizures
- reduction of seizures
- Seizure control. [PATIENT] (4 yr. old) was having 5-10 seizures a week before Medical Cannabis. She is down to a 7 week period seizure free- and if she has one it is every couple of weeks and very small.
- Seizure control is my greatest benefit but it also helps with the migraines from a lit of broken skull.
- seizure free
- Seizures and anxiety, depression, and better sleep better

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- Seizures anxiety depression bi-polar
- Seizures are less intense
- -Stopped shaking hands (side effect from epilepsy meds).
 - FEWER SEIZURES. ***If this was more affordable I am very confident they would stop all together because I would be able to use more.
 - Helps w/nausea (side effect from epilepsy meds).
 - Reduces an
- the ability to control my pain management without the groggy feeling I get when I use pain medication.
- The decrease in the number of daily seizures
- The treatment stops my seizure from being so frequent it helps my eating and gives me great relief thank you for finding something that really helps me thank you all for supporting other epileptic patients
- This is typed by his spouse. [PATIENT] has a TBI (traumatic brain injury). He says that it has had a major beneficial effect on his quality of life. One of the unexpected side effects has been a clarity of thought. He use to get confused doing some small tasks and some how it helps him to think clearer. He has been exceedingly more motivated and accomplishing more.
- We have seen a great deal of improvement on our daughters ability to focus and attend to tasks. if this improvement is due to a reduction in subclinical seizures or other factors is yet to be seen. We will have a follow up EEG in a few months to see if we are getting subclinical seizure control.
- We haven't noticed any new seizures.
- [PATIENT] is no longer on cannabis - sorry

Crohn's Disease

3

- It helps me with sleep

4

- Helping calm my intestines.
- rest and more solid stools
- slightly improved mood, moderate pain relief

5

- 1. Decrease in Anxiety
- 2. Increase in Appetite
- 3. Decrease in Pain
- 4. Decrease in Nausea
- A recent blood test showed C Reactive Protein at 2.2, in Nov 2015 it was greater than 20. Also helps with anxiety.
- less bowel pain and bowel movement pain

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- Medical cannabis has allowed me to sleep well at night. I was up 3-4x/night- now I sleep through the night. This allows me to feel significantly better during the day. less fatigue and less arthritic pain and so I've been able to significantly cut back on opiate pain meds.
- Pain Management
- Pain relief.
- Sleeping better , allowing for more energy. Lower anxiety.
- The cannabis has allow me to maintain my weight more effectively. Pain relief from cramping would also be a benefit.

6

- A large reduction in symptoms, allowing me to participate in my daily life without a large number of limits my symptoms would place on me - stools decreased from over 8 a day to about 2 with much less blood and mucous in stools. Pain has reduced to a tolerable amount.
- Being able to sleep.
- Decrease in pain, reduced symptoms, completely able to avoid having to use narcotics for pain relief
- decreased anxiety, decreased pain
- Helps to lower stress, my muscle spasms have been pretty much nulled! My stomach issues having been like before, cramps have been minimized, just feel quite a bit better!
- I have gained an amount of weight that I have not been able to in the past. I have been very pleased with this result.
- Increased stool firmness
- My stomach (core) feels more normal (calm) and my bowel movements are less often - have more form - not as much liquid & gas.
- nausea control
- Pain relief in low back
- Pain relief is the biggest benefit. Also less cramping.
- pain/appetite management
- Reduction in the use of pain medications

7: Great Deal of Benefit

- abdominal pain relief
- Better Health
- Can digest better so im not scared to eat goving me more energy allowing me to accomplish more in a day sleep better at night joint pain relief cramping relief clears up mental fogginess less agitation eases anxiety
- Cannabis has helped with keeping the chrons calm. I made it through the holidays with no flare ups.
- Helped reduce swelling in my ankle a great deal, among other benefits

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- Helps in overall feeling much better, reduces abdominal cramping tremendously, helps w/ nausea. I also use the medication after my Remicade treatments as usually after those treatments I don't feel well. I use the cannabis and it's almost instant relief. The medical cannabis over all makes me feel much better than when not using the medication.
- I am in significantly less pain. I can function throughout the day so much better than I could before the cannabis program. It is like night and day.
I have less dizziness from vertigo with the cannabis
I have better mobility of my neck
- I have gone from having diarrhea daily, to having it once a month. That's a huge quality of life improvement for me.
- It stops vomiting almost as quickly as IV drugs for nausea
- Just a general improvement of quality of life with the symptoms of my Crohn's disease. I have extremely benefited from cannabis.
- Less nausea
- Lessens the amount of stools per day. Increases my appetite so that I can maintain my weight. Allows me to digest my food slower increasing the amount of nutrition absorbed.
- My overall inflammation has dropped significantly thanks to medical cannabis. this has resulted in me having to drop my daily amount of background (Lantus) insulin throughout the day by 10 units. with my diabetes, I am less insulin resistant and probably use 15 units less per day on top of the 10 units less per day from my Lantus. I also have been sleeping much better and am have been able to completely remove opiates from my life which is a huge accomplishment for me.
- No crohns disease flare ups since starting treatment
- Not having to live with daily pain since starting treatment!!!!!! :-)
- pain killers have been eliminated from my routine because pain has been reduced
- Pain relief
- Pain relief
- reduced diarrhea - reduced stomach pain, gas and bloating
- Re-established my ability to partake in physical activity.
- Relief from pain and nausea. Help with sleeping.
- Suppression of most of my Crohn's symptoms with very few side effects
- That the pain was pretty much non-existent.
- The medicine has helped me not feel as sick all the time.
- the Vape oil allows me to go to work without vomiting. also the pills help with inflammation and pain
- When I was on it the quality of life it gave me back

Terminal Illness

4

- helps with pain

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- Helps with sleep. Helps with pain.
- Nausea and vomiting

5

- [PATIENT] is dead. But it kept his potential nausea very low and help with any potential pain.
- Pain relief, distraction from pain

6

- I'm comfortable and able to eat and sleep
- it really helpful with my anxiety and rib pain
- Might save my life
- Reduction of Nausea and pain, and increase in appetite.
- Seizures have dissipated
Somewhat calmer behavior

7: Great Deal of Benefit

- Ability to create appetite and relieve pain
- Anti nausea, it's a miracle worker for nausea.
- Coping with nausea, being able to eat and maintain weight
- [PATIENT] has passed away. I am her daughter and was her care giver. She was open to trying medical cannabis and we got the liquid form. It was a saving grace. She was in a lot of pain and when prescribed medications did NOT work - we started this and it kept her calm and relaxed. I am very thankful that we were able to have this option available. It helped to make her last months more bearable and truly it would have been miserable without it.
- Eating
- general overall feeling of well-being...pain relief
- Getting appetite back, and attitude adjustment.
- Helps a lot with pain and relaxing from stress also helps a lot with upset stomach.
- Improved quality of sleep.
- It helps a lot with my pain level. Since I started this program I have not needed to increase my opioid medication to control my pain. I many times use the vaporizer in place of oxycodone for breakthrough pain. When my anxiety is very hi I use the vaporizer. It has made a very positive difference in my quality of life at this point.
- my nausea after chemo is gone in less than a minute after one inhalation from my vaporizer
- No nausea from Chemotherapy. Much more energy and appetite along with a more positive outlook on life.
- Pain relief
- reduced vomiting.
- Relaxing, peaceful sleep and wake up relaxed... less anxiety..
- Relief from nausea

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- since I've started using the oil my brain cancer has maintained its size, it isn't getting any bigger and it isn't getting any smaller.
- the relief of pain.
- We have seen a girl go from not interacting, to interacting. No appetite to appetite. Balance also seems better.

HIV/AIDS

3

- Eating
- That the medicine does increase the ability to tolerate my intense pain, or at least takes some of the edge off.

4

- Takes the edge off of the worst pain, not quite as sharp on most days.

6

- It has significantly helped reduced the physical pain related to my chronic pain, fibromyalgia, and systemic exertion intolerance disease. It has helped make my days more bearable and easy.
- Less pain, better sleep and I experience less anxiety.
- Pain management

7: Great Deal of Benefit

- Relief that my other pain medication does not remedy.
- A significant reduction in after-medication nausea. There has also been relief of neuropathic pain in my extremities.
- able to sleep at night. I have been living with Neuropathy pain since 1990
- Appetite, was losing weight fast! Didn't have one! Now got it back! And gained 20 pounds! From this.
- calmness
- Cannabis has been a helpful tool in finding relief from pain and fatigue; so that I'm able to exercise and do yoga. I'm able to eat and I have gained back healthy weight. I have found cannabis to be beneficial in relieving anxiety and depression, also. Although, I think there are medicinal qualities in the whole flower that are missed in the current extractions available.
- Finally putting on weight again due to underlying health reasons that he has trying to overcome for 20+ years, finally gaining fat mass back, started as a skeptic, no effect from leaf form tries
- Help with nausea
- Immediate relief of nausea and the ability to sleep at night.
- Reduction in spasms
- relaxed no anxiety stomach better neuropathy better
- stress/mental stability, medication toxicity dampening (less effect on stomach), better quality sleep, longer sleeping time, pain decreased, food consumption increase.

APPENDIX A: PATIENT REPORTED BENEFITS FROM SURVEYS

- The constant pain in my feet is really diminished and only have occasional time that I feel like I am having hot nails slammed into them

Tourette Syndrome

4

- calmer in general
tics have reduced some
doesn't get upset as easily by noise
more regular BM's
gained some weight - more hungry
- The normalization of cannabis, cannabis's new legal status and increased social acceptance.

5

- The cannabis has calmed both physical and verbal tics. It has not completely suppressed the tics.

6

- elimination of tic behaviors
- [PATIENT] has experienced decreased anxiety and rigidity related to his autism. He is better able to focus and pay attention. His mood is more positive and he is more flexible.
- My tourettes has calmed down.
- Quiets the tourette symptoms.
- Reduced ticks, better cognition, calmer in public places, Reduced stress over all.

7: Great Deal of Benefit

- [PATIENT] has greatly reduced tics and anxiety which has improved every aspect of his life.
- less ticks, no depression, focus at work
- No longer injuring herself. Such as banging head and kicking walls and etc. Does not seem to be uncomfortable.
- Reduced motor and vocal tics tremendously. I am off 6 medications including morphine.
- The removal of my disability, Tourette Syndrome. And it's almost all gone, when medicated.
- Within 1 week of use, my tics disappeared and have stayed gone even with occasional use. This has never happened previously in my life, so it is very effective.

Glaucoma

6

- Less eye pressure headaches
Increased appetite
Less anxiety

7: Great Deal of Benefit

- reduction of interocular eye pressure; also reduction in muscle cramps and chronic pain
- spasm relief
- Reduced eye pressure especially during pressure attacks and quick climbs, pain relief and addresses the migraines associated with my glaucoma (brain injury related)....I also remain seizure free
- Better quality of life, greatly reduced pain, greatly reduced spasms and exacerbations, less stiffness able to sleep through the night.
- Pain and encumbered vision from Iritis Uvitis completely eliminated - Have been able to discontinue use of Pred Forte steroids which had terrible side effects but was prior to medical cannabis the thing drug available for managing the pain and inflammation and white cell production associated with my disease.
- The reduction of symptoms of my glaucoma. Less frequent eye pain attributed from lower IOP.
- verification that cannabis can treat my qualifying conditions.

ALS

4

- It helps alleviate my stress.

5

- help with sleep, anxiety and regularity

6

- helps calm mind/nerves, this lowers stress which caused muscle twitching
- Less pain
- Spasticity relief

7: Great Deal of Benefit

- anxiety is greatly reduced
- I can sleep at night, all night long.
- Pain control (back pain) and no leg cramps
- The relief from pain
The feeling of well being

Minnesota Medical Cannabis Program: Patient Experiences from the First Program Year

Minnesota Medical Cannabis Program: Patient Experiences from the First Program Year

Minnesota Department of Health
Office of Medical Cannabis
PO Box 64882
St. Paul, MN 55164-0882
651-201-5598 (Metro) or 844-879-3381 (Non-metro, toll-free)
Health.Cannabis@state.mn.us
www.health.state.mn.us

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Upon request, this material will be made available in an alternative format such as large print, Braille or audio recording. Printed on recycled paper.

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Executive Summary

In May 2014, Minnesota became the 22nd state to create a medical cannabis program. Distribution of extracted cannabis products in liquid or oil form to qualified, enrolled patients began July 1, 2015. Minnesota's medical cannabis program is distinct from those in nearly all other states as the Minnesota Department of Health's Office of Medical Cannabis is required to study and learn from the experience of participants. This report draws on data from enrollment, purchasing and related health information, and survey results to describe the experience of patients who enrolled during the first year of the program's operation: July 1, 2015 through June 30, 2016.

The Office of Medical Cannabis anticipates performing additional analyses of data for the first year cohort of enrolled patients, as well as initiating analyses of data from patients who enrolled in the program later. Of particular interest are patients who enrolled after intractable pain became a qualifying condition on August 1, 2016. A report is planned for the end of 2017 that will give a preliminary look at the experience of the first several hundred patients certified for intractable pain. It is possible that focused projects will be developed in the future that will draw on medical record information to answer specific questions raised by analyses of the kinds of program data described in this report.

Participation

Between July 1, 2015 and June 30, 2016 a total of 1660 patients enrolled in the program and 577 health care practitioners registered themselves in order to certify that patients have a medical condition that qualifies them for the program. The most common qualifying conditions were severe and persistent muscle spasms (43%), cancer (28%), and seizures (20%). Each of the remaining six qualifying conditions during the first year – Crohn's Disease, Terminal illness, HIV/AIDS, Tourette Syndrome, glaucoma, and ALS – accounted for less than 10% of patients. Ten percent (167 patients) were certified for more than one qualifying condition. Most patients were middle-aged (56% between ages 36-64), 11% were <18, and 11% were ≥65. Distribution by race/ethnicity generally matched the state's demographics, with 90% of patients describing themselves as white.

The legislation that established the program specified there would be one location for purchasing medical cannabis (called Cannabis Patient Centers; CPCs) in each of the state's eight congressional districts. Patients who enrolled in the program during the first year came from throughout the state, with the average distance from the patient's home to the nearest CPC 29 miles (median distance=16 miles). Some patients were a considerable distance from the nearest CPC, however, with 13% over 60 miles from the nearest one. The program allows patients to have one or more parents or non-parent caregivers who register with the program, who are then allowed to transport and administer a patient's medical cannabis. Only 11%

of patients had a registered caregiver, 17% had a registered parent or guardian, and 26% had either a registered parent/legal guardian or a registered caregiver.

Among the 577 health care practitioners who registered with the program 82% were physicians, 13% were advanced practice registered nurses, and 5% were physician assistants.

Medical Cannabis Purchasing Patterns

Most patients make their first medical cannabis purchase within 14 days of program approval. Subsequent purchases typically follow a roughly monthly periodicity. However, intervals between purchases are sometimes less than a month, especially during the first months of program participation as the patient experiments with small amounts of different products. And intervals between purchases are sometimes much longer than a month. Using a cutoff of six months without any medical cannabis purchases as a surrogate for program discontinuation, 51% of patients who enrolled and made a purchase within the first six months of the program discontinued participation in the program as of December 31, 2016.

Medical Cannabis Use Patterns

Each patient's medical cannabis purchasing transactions during their first enrollment year (or through early March if still within their first enrollment year) were analyzed. A total of 16,238 products were purchased during 10,898 transactions, with 38% of all transactions consisting of two or more products. For analytic purposes, products were classified according to the ratio of delta-9-tetrahydrocannabinol (THC) to cannabidiol (CBD) as follows: Very High THC:CBD (100:1 or higher), High THC:CBD (>4:1 up to 99:1), Balanced THC:CBD (1:1 up to 4:1), High CBD:THC (\geq 1:1 up to 99:1), and Very High CBD:THC (100:1 or higher).

Products for enteral administration (swallowed – includes capsules and oral solutions) and products for inhalation (vaporized oil) each accounted for 45% of product purchases. Products for oromucosal administration (absorption through cheek) accounted for 9%. Nearly 50% of all purchases were Very High THC:CBD products, followed by Balanced THC:CBD (30%) and High CBD:THC (15%). Very High THC:CBD products were most commonly oil for vaporization or for oromucosal absorption, while Balanced THC:CBD and High CBD:THC products were most often for enteral administration.

Examining purchasing history across all patients is very complex for reasons that include experimentation with different products over time. As a first approach to assessing routine use of products, most frequently purchased products were examined for each patient. For 28% of patients, two or more products were purchased the same number of times. The product types that emerged as most frequently purchased were Very High THC vaporization oil (25%), High CBD:THC enteral preparations (14%), and Balanced enteral preparations (13%). Most frequently purchased product types varied considerably across medical conditions.

Benefits

Information on patient benefits comes from the Patient Self-Evaluations (PSE) completed by patients prior to each medical cannabis purchase and from patient and health care practitioner surveys. Results of analysis of PSE and survey data indicate perceptions of a high degree of benefit for most patients.

Patients responded to a survey question asking them how much benefit they believe they received from using medical cannabis on a scale from 1 (no benefit) to 7 (great deal of benefit). Across all patients 64% indicated a benefit rating of 6 or 7 and this degree of benefit was indicated by at least half of the patients with each medical condition. A small but important proportion of patients indicated little or no benefit: 9% gave a rating of 1, 2, or 3. Benefit ratings varied somewhat by qualifying medical condition. When patients were asked what the most important benefit was for them, two-thirds indicated a reduction in symptoms directly related to their qualifying medical condition and most of the remainder indicated more general quality of life benefits.

An important part of this report is the verbatim comments written by patients, and the reader is encouraged to review these comments, presented in an Appendix. Examples of these comments include:

- “Almost all muscle spasm and pain associated with spasms are gone. I used to have constant nerve triggered pain that is minimal now. Results were almost immediate. I am sleeping way better now also.”
- “[NAME] has passed away. I am her daughter and was her care giver. She was open to trying medical cannabis and we got the liquid form. It was a saving grace. She was in a lot of pain and when prescribed medications did NOT work – we started this and it kept her calm and relaxed. I am very thankful that we were able to have this option available. It helped to make her last months more bearable and truly it would have been miserable without it.”
- “I am getting enough sleep for the first time since about 2011. My absence seizures have gone from 3-4 a day to almost 0. It also has lessened the severity of grand mal seizures. The recovery time after has gone from around 12 hours to around 4.”
- “At first it helped a lot but my seizures have returned.”
- “Spasms – only a little better.”

Health care practitioners were somewhat more conservative in assessment of benefit to their patients. Across all the benefit ratings by health care practitioners, 38% indicated a rating of 6 or 7 and 23% indicated little or no benefit (rating of 1, 2, or 3). Similarity in benefit assessment between health care practitioners and patients appears to vary by medical condition, with highest discrepancy among seizure patients. Descriptive comments suggest at least part of the difference is driven by perspective of what constitutes benefit. The patients cite quality of life

benefits more often than the health care practitioners, who appear to focus more on objective measures such as seizure counts.

The symptom scores provided in the Patient Self-Evaluation data have the advantage of completeness, since they are required prior to each medical cannabis purchase. In this report a reduction of $\geq 30\%$ was applied to most symptoms to indicate clinically meaningful symptom reduction. Results show patterns similar to those in the survey benefits rating, but usually somewhat smaller in size. For most symptoms between half and two-thirds of patients who achieve clinically meaningful improvement retained that degree of improvement over the next four months.

Examples of proportion of patients achieving and retaining $\geq 30\%$ symptom reduction include:

- Among seizure patients, 68% reported $\geq 30\%$ reduction in seizure frequency and 49% both achieved that level of reduction and retained it, on average, for at least four months
- Among patients with Tourette syndrome, 61% reported $\geq 30\%$ reduction in tic frequency and 46% both achieved that level of reduction and retained it, on average, for at least four months
- Among patients with Crohn's disease, 51% reported $\geq 30\%$ reduction in number of liquid stools per day and 29% both achieved that level of reduction and retained it, on average, for at least four months
- Among patients with severe, persistent muscle spasms, 48% reported $\geq 30\%$ reduction in spasm frequency and 28% both achieved that level of reduction and retained it, on average, for at least four months
- Among cancer patients with at least moderate levels of nausea when they started using medical cannabis, 38% reported $\geq 30\%$ reduction of nausea and 23% both achieved that level of reduction and retained it, on average, for at least four months
- Among cancer patients with at least moderate levels of pain when they started using medical cannabis, 29% reported $\geq 30\%$ reduction of pain and 12% both achieved that level of reduction and retained it, on average, for at least four months

Moderate to severe levels of non-disease-specific symptoms such as fatigue, anxiety, and sleep difficulties were common across all the medical conditions. And the reductions in these symptoms was often quite large. These findings support the understanding that some of the benefit perceived by patients is expressed as improved quality of life.

The type(s) of medical cannabis used at the time patients achieved clinically significant improvement was analyzed for each symptom assessed within each category of medical condition. Full results of these analyses are presented in an Appendix and summaries are in the Benefits chapter.

Adverse Side Effects

At this point, the safety profile of the medical cannabis products available through the Minnesota program seems quite favorable. Approximately 20-25% of enrolled patients report negative physical or mental side effects of some kind, with the majority – around 60% - reporting only one and 90% reporting three or fewer. The vast majority of adverse side effects, around 90%, are mild to moderate in severity. An assessment of the 30 patients reporting severe side effects, meaning “interrupts usual daily activities,” found no apparent pattern of patient age, medical condition, or type of medical cannabis used. The most common adverse side effects are dry mouth, drowsiness, and fatigue. Fortunately, up to the present no serious adverse events (life threatening or requiring hospitalization) have been reported.

Affordability and Suggestions for Improving the Program

Unlike traditional pharmaceuticals whose costs are often covered through insurance reimbursement, medical cannabis purchased through the Minnesota program is currently not covered by insurance and must be purchased out of pocket. The patient survey asked for a rating of product affordability on a scale of 1 (very affordable) to 7 (very prohibitive). More than half (51%) responded with a 6 or a 7 and 86% responded with a score of 4 or higher. “Bring the costs down” was a frequent response when patients and certifying health care practitioners were asked how the program could be improved. Some patients indicated on surveys they used less medical cannabis than they knew was helpful to them because they could not afford it.

1. Introduction

In May 2014, Minnesota became the 22nd state to create a medical cannabis program. Distribution of cannabis products to qualified, enrolled patients began July 1, 2015. Minnesota's medical cannabis program is distinct from those in nearly all other states due to the fact that the Minnesota Department of Health's Office of Medical Cannabis is required to study and learn from the experience of participants. Minnesota's online registry, which integrates information from patients, certifying health care practitioners and manufacturers, continuously captures program data. Data elements from the Registry have been selected to create a de-identified research data set for reporting and research. This report draws on aspects of that research data set to describe the experience of patients who enrolled during the first year of the program's operation: July 1, 2015 through June 30, 2016.

Data in this report come from several aspects of the program's operations:

- Information from registration or enrollment of patients, health care practitioners, and caregivers;
- Information patients provide each time they visit a cannabis patient center for purchase of cannabis products, including information on symptom severity and side effects;
- Details about each cannabis product purchased; and
- Information is derived from responses to periodic surveys of patients and their certifying health care practitioners.

Though there is certainly imprecision in some of the data collected by the program, this report provides important details that can be found in few other states. A notable part of the report is a set of statements regarding benefits, negative effects, and comments about the program made by patients and health care practitioners. These are redacted to protect privacy, but otherwise presented as was written on the surveys. The comments have been coded by type but the verbatim comments have a power of their own, reminding us that each enrollee is a unique individual, not just a number. A few comments are included elsewhere, but the reader is encouraged to spend time reviewing the full listing of responses in the appendices.

The Office of Medical Cannabis anticipates performing additional analyses of data for the first year cohort of enrolled patients, as well as initiating analyses of data from patients who enrolled in the program later. Of particular interest are patients who enrolled after intractable pain became a qualifying condition on August 1, 2016. A report is planned for the end of 2017 that will give a preliminary look at the experience of the first several hundred patients certified for intractable pain. It is possible that focused projects will be developed in the future that will

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draw on medical record information to answer specific questions raised by analyses of data derived from the program registry.

2. Patients and Caregivers Registered in the First Program Year

DESCRIPTION OF PATIENTS ENROLLED IN THE FIRST PROGRAM YEAR

Qualifying Condition

During the first year of the Minnesota Medical Cannabis program (July 2015-June 2016), 1,660 patients were certified by registered healthcare practitioners and subsequently enrolled in the program (Figure 2.1). The healthcare practitioners certified the patients as having one or more of the following qualifying conditions: severe and persistent muscle spasms (n=713), cancer (n=468), seizures, including those characteristic of epilepsy (n=328), Crohn's disease (n=108), terminal illness (n=94), HIV/AIDS (n=54), Tourette syndrome (n=30), glaucoma (n=24), and amyotrophic lateral sclerosis (ALS) also known as Lou Gehrig's disease (n=22) (Table 2.1, Figure 2.2). Of the 1660 patients from the first program year, 167 (10.1%) were certified as having more than one qualifying condition; these patients are represented more than once in Table 2.1 and Figure 2.2.

Figure 2.1. Patient enrollment in the first program year.

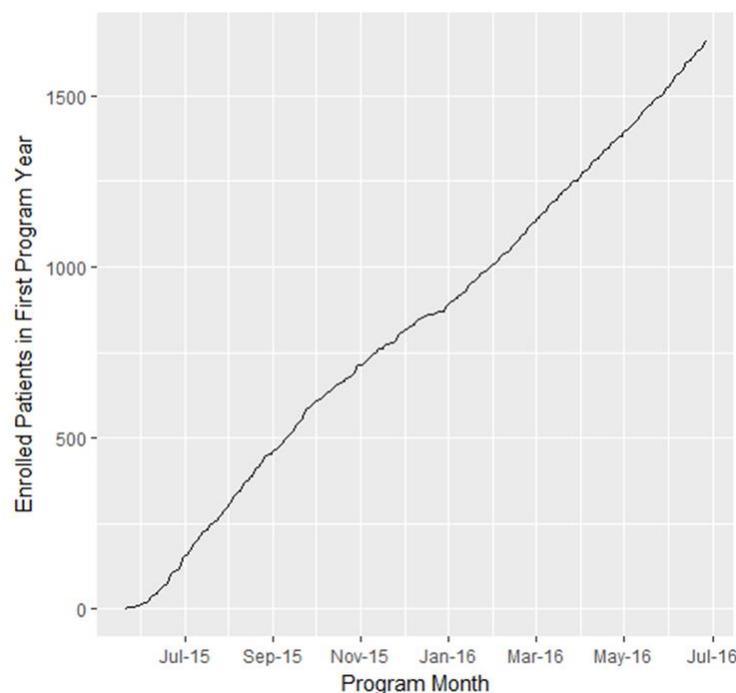
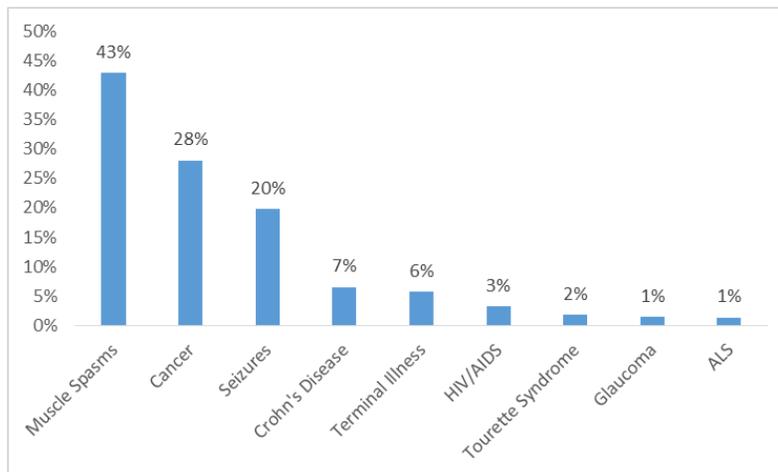


Table 2.1. Patient counts by qualifying condition.

Condition	Count	%
<i>Muscle Spasms</i>	713	43%
<i>Cancer</i>	466	28%
<i>Seizures</i>	328	20%
<i>Crohn's Disease</i>	108	7%
<i>Terminal Illness</i>	94	6%
<i>HIV/AIDS</i>	54	3%
<i>Tourette Syndrome</i>	30	2%
<i>Glaucoma</i>	24	1%
<i>ALS</i>	22	1%

Note: Percentages sum to more than 100 percent because among the 1660 patients enrolled during the first year, 167 (10.1%) were certified for more than one qualifying condition.

Figure 2.2. First year cohort patients by qualifying medical condition.



Note: Percentages sum to more than 100 percent because among the 1660 patients enrolled during the first year, 167 (10.1%) were certified for more than one qualifying condition.

Age and Gender

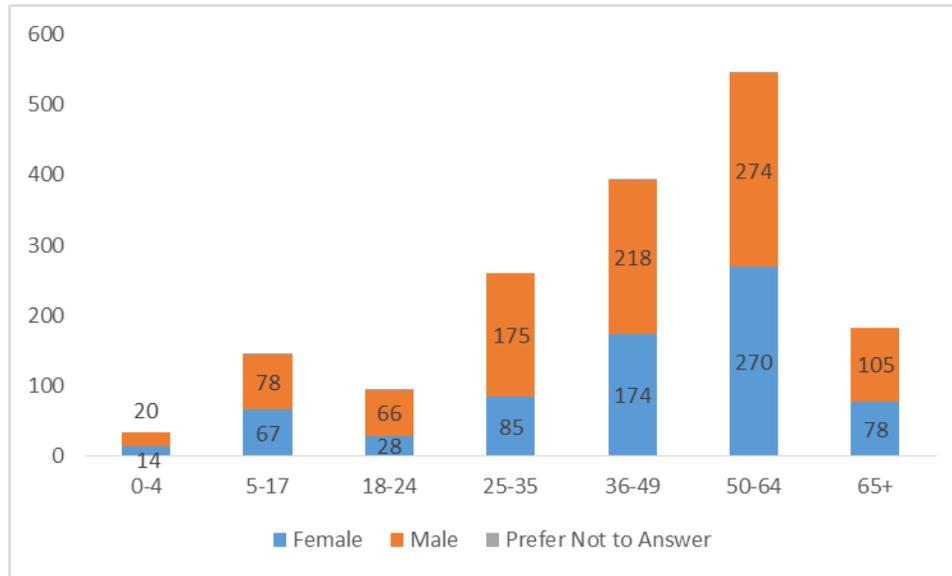
At the time of certifying that a patient has a medical condition qualifying them for the medical cannabis program, the certifying healthcare practitioner enters the patient’s date of birth. Additionally, during registration, patients are asked to report gender and race/ethnicity but are not required to do so. Table 2.2 shows the breakdown of patients by age category and gender at the time of initial program enrollment. The gender breakdown of patients in the first program year was 57% male and 43% female, with <1% of patients declining to report gender. Patients tended to be middle-aged, with 56.3% of the cohort falling between ages 36-64. However, the cohort also included a notable proportion of pediatric patients (10.7%) and patients over 65 years (11.0%).

Table 2.2. Patient counts by age and gender.

	0-4	5-17	18-24	25-35	36-49	50-64	65+
Female	14 (41%)	67 (46%)	28 (29%)	85 (33%)	174 (44%)	270 (49%)	78 (43%)
Male	20 (59%)	78 (53%)	66 (69%)	175 (67%)	218 (55%)	274 (50%)	105 (57%)
Prefer Not to Answer	0 (0%)	1 (1%)	2 (2%)	0 (0%)	2 (1%)	3 (1%)	0 (0%)
Total	34 (2%)	146 (9%)	96 (6%)	260 (16%)	394 (24%)	547 (33%)	183 (11%)

Note: Percentages are calculated based on the total count of patients in each age category.

Figure 2.3. Age and gender breakdown of first year cohort.



Age by Qualifying Condition

Breakdown of age category within each qualifying condition is shown in Table 2.3. Among the first year cohort, average age was 44.3 ± 18.9 years. Age distribution varied substantially across qualifying medical condition groups; patients certified for glaucoma or ALS tended to be older in general (average age of 60.4 ± 14.0 and 61.5 ± 9.6 , respectively); patients certified for seizure disorders or Tourette syndrome generally were younger (23.4 ± 16.0 and 25.3 ± 11.7 , respectively).

Table 2.3. Patient age by qualifying medical condition.

	0-4	5-17	18-24	25-35	36-49	50-64	65+	Mean Age (SD)	Total
Muscle Spasms	3 (0%)	6 (1%)	33 (5%)	124 (17%)	216 (30%)	268 (38%)	63 (9%)	47.3 (14.5)	713
Cancer	3 (1%)	15 (3%)	11 (2%)	33 (7%)	83 (18%)	217 (47%)	104 (23%)	54.6 (16.2)	466
<i>Pain</i>	1 (0%)	3 (1%)	8 (3%)	26 (8%)	65 (20%)	151 (47%)	66 (21%)	54.3 (15.3)	320

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	0-4	5-17	18-24	25-35	36-49	50-64	65+	Mean Age (SD)	Total
<i>Nausea/Vomiting</i>	1 (0%)	12 (4%)	10 (4%)	18 (7%)	50 (18%)	130 (48%)	52 (19%)	53.4 (16.5)	273
<i>Cachexia/Wasting</i>	1 (1%)	6 (3%)	5 (3%)	8 (4%)	16 (9%)	90 (50%)	54 (30%)	57.9 (16.5)	180
Seizures	30 (9%)	114 (35%)	43 (13%)	68 (21%)	52 (16%)	18 (6%)	3 (1%)	23.4 (16.0)	328
Crohn's Disease	0 (0%)	0 (0%)	9 (8%)	35 (32%)	35 (32%)	22 (20%)	7 (7%)	41.4 (13.8)	108
Terminal Illness	2 (2%)	9 (10%)	3 (3%)	8 (9%)	20 (21%)	38 (40%)	14 (15%)	48.7 (20.1)	94
<i>Pain</i>	0 (0%)	7 (11%)	1 (2%)	6 (9%)	16 (24%)	27 (41%)	9 (14%)	48.7 (20.1)	66
<i>Nausea/Vomiting</i>	1 (2%)	4 (9%)	2 (4%)	3 (7%)	9 (20%)	21 (47%)	5 (11%)	48.7 (20.3)	45
<i>Cachexia/Wasting</i>	1 (3%)	4 (11%)	2 (5%)	1 (3%)	3 (8%)	19 (50%)	8 (21%)	48.9 (20.3)	38
HIV/AIDS	0 (0%)	0 (0%)	0 (0%)	8 (15%)	20 (37%)	26 (48%)	0 (0%)	47.0 (9.7)	54
Tourette Syndrome	0 (0%)	11 (37%)	3 (10%)	12 (40%)	3 (10%)	1 (3%)	0 (0%)	25.3 (11.7)	30
Glaucoma	0 (0%)	0 (0%)	1 (4%)	0 (0%)	4 (17%)	11 (46%)	8 (33%)	60.4 (14.0)	24
ALS	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (9%)	12 (55%)	8 (36%)	61.5 (9.6)	22

Race and Ethnicity

Table 2.4 shows patient-reported race and ethnicity. Patients were given the option to select multiple race and ethnicity categories, so the counts reflect some patients more than once. Ninety-one patients selected more than one race/ethnicity and 95 patients declined the question. Compared to 2014 Census Bureau estimates of race/ethnicity in Minnesota, the distribution of responding members of the first program year cohort is generally similar, with a slightly higher proportion of American Indians (2.7% versus 1.9%) and lower proportion of Hispanics (2.4% versus 4.9%) and Asians (1.7% versus 5.0%).

Table 2.4. One-year cohort patient race and ethnicity compared to overall state demographics.

Race/Ethnicity	Medical Cannabis Registry	2014 Census Bureau Estimates
American Indian	42 (2.7%)	1.9%
Asian	27 (1.7%)	5.0%
Black	101 (6.5%)	6.5%
Hawaiian	3 (0.2%)	0.1%
White	1410 (90.1%)	87.5%
Hispanic	37 (2.4%)	4.9%
Other	26 (1.7%)	1.7%

Race and ethnicity estimates for Minnesota can be found at the following website:
<http://factfinder.census.gov/faces/nav/jsf/pages/index.xhtml>

Registered Caregivers and Parents/Legal Guardians

If a patient is unable to pick up their medication from a cannabis patient center or is unable to administer the medication, their certifying health care practitioner may also certify the patient's need for a designated caregiver. This allows the enrolled patient to have a caregiver who then undergoes a background check and registers with the program. Registered caregivers can then legally obtain and possess the patient's medical cannabis on their behalf. Additionally, parents or legal guardians of patients can register with the program to act as caregiver and pick up or possess medication on behalf of the patient. Table 2.5 shows the proportion within each

qualifying condition group of patients who have registered caregivers or parents or legal guardians registered to pick up medication on behalf of the patient. Patients certified for ALS, cancer, or terminal illness have the highest proportions of patients with registered caregivers (32%, 15% and 15%, respectively). Patient certified for seizure disorders or Tourette syndrome, who are also generally younger than the cohort at large, have the highest proportion of patients with registered parents or legal guardians in the program (65% and 53%, respectively). Patients with seizures or Tourette syndrome also have the highest proportion of either registered caregivers or registered parents/legal guardians. Table 2.6 shows the absolute number of registered caregivers associated with a patient in the first year cohort, reported by condition. Most patients with registered caregivers have only one caregiver able to pick up medication on their behalf (n=157); 21 patients have two caregivers and one patient has three caregivers.

Table 2.5. Proportion of patients with registered caregivers, parents or legal guardians authorized to pick up medication, or both.

CONDITION	Number of Enrolled Patients	Patients with Registered Caregiver(s)	Patients with Registered Parent(s)/Legal Guardian(s)	Patients with Registered Caregiver(s) or Parent(s)/Legal Guardian(s)
All Conditions	1660	179 (11%)	279 (17%)	430 (26%)
Cancer	466	71 (15%)	23 (5%)	92 (20%)
Terminal Illness	94	14 (15%)	10 (11%)	22 (23%)
Glaucoma	24	3 (13%)	0 (0%)	3 (13%)
HIV/AIDS	54	1 (2%)	0 (0%)	1 (2%)
Tourette Syndrome	30	2 (7%)	16 (53%)	16 (53%)
ALS	22	7 (32%)	1 (5%)	8 (36%)
Seizures	328	32 (10%)	213 (65%)	225 (69%)
Muscle Spasms	713	72 (10%)	26 (4%)	96 (13%)
Crohn's Disease	108	6 (6%)	3 (3%)	8 (7%)

Table 2.6. Count of registered caregivers associated with patients enrolled in the first program year, by qualifying condition.

Condition	Registered Caregiver Count
All Conditions	202
Cancer	83
Terminal Illness	19
Glaucoma	4
HIV/AIDS	1
Tourette Syndrome	2
ALS	7
Seizures	37
Muscle Spasms	79
Crohn's Disease	6

Geographic Distribution and Distance to Nearest Cannabis Patient Center

At the time of registration, patients provide their home address for verification of Minnesota residency. Home addresses are retained in the patient’s online registry account but are not retained in the research database; in lieu of home address, patient ZIP codes and calculated distances from each address to the nearest cannabis patient center are accessible for research purposes. The general geographic distribution of patients was examined using patient-reported ZIP codes; the first three digits of ZIP codes compose a prefix which corresponds to an approximate geographic region¹. The U.S. Postal Service assigns to each prefix labels that match

¹ <http://pe.usps.com/Archive/HTML/DMMArchive20050106/print/L002.htm>

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the major city within the region and approximate surrounding cities; these region labels are shown in Table 2.7, along with the count of patients living in the corresponding ZIP codes.

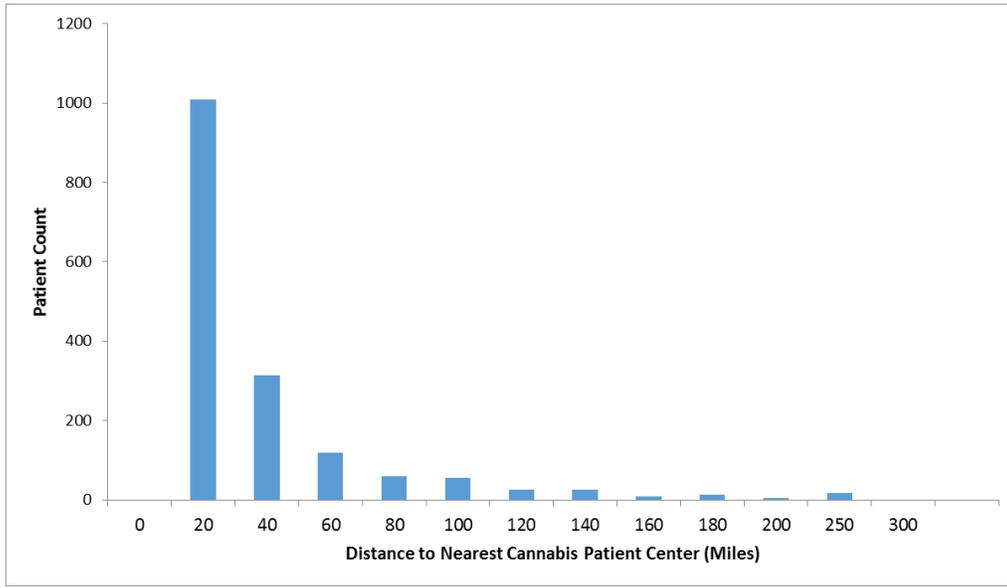
Table 2.7. Geographic distribution of patients by ZIP code prefix.

Region	ZIP Code Range	Patient Count (%)
St Paul	55000-55199	561 (34%)
Minneapolis	55300-55599	671 (40%)
Duluth	55600-55899	59 (4%)
Rochester	55900-55999	104 (6%)
Mankato	56000-56199	63 (4%)
Willmar	56200-56299	49 (3%)
St Cloud	56300-56399	80 (5%)
Brainerd	56400-56499	27 (2%)
Detroit Lakes	56500-56599	28 (2%)
Bemidji	56600-56699	11 (1%)
Grand Forks*	56700-56799	7 (0%)

Note: The Grand Forks region, corresponding to ZIP codes with a 567 prefix, refers to a region including Grand Forks, South Dakota, as well as several ZIP codes located in Minnesota near the western border. Patients living in this region reside in Minnesota.

Two medical cannabis manufacturers each operate four cannabis patient centers where patients can purchase medical cannabis following consultation with pharmacy staff at the center. Minnesota law required that one cannabis patient center be open in each of Minnesota’s eight legislative districts by July 1, 2016 (one year after the program start date). Figure 2.4 shows the distribution of calculated one-way distance from each patient’s home address to the nearest cannabis patient center location as of July 1, 2016, when all eight centers were operational. Average one-way distance is 28.9 ± 36.9 miles; median one-way distance is 15.5 miles. The majority of patients ($n=1441$; 86.8%) live within 60 miles of the nearest cannabis patient center.

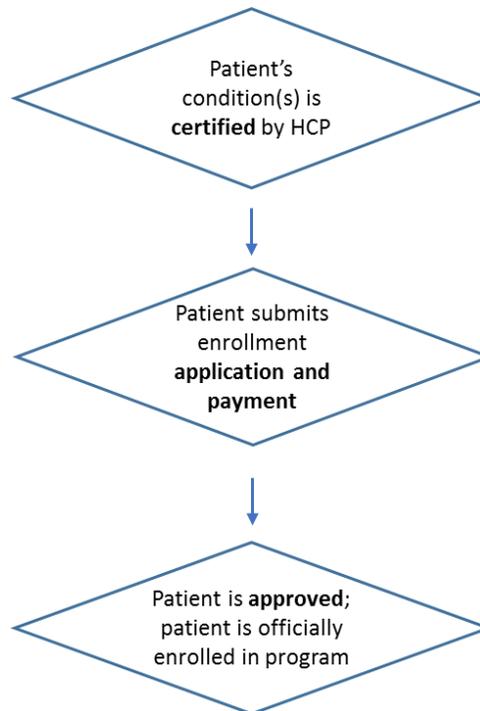
Figure 2.4. Distribution of one-way distance from patient home to nearest cannabis patient center.



From Certification to Program Approval: How Long Does it Take for Patients?

A sequential series of steps are followed in order to move patients from certification by a healthcare practitioner to their enrollment in Minnesota’s Medical Cannabis program. First, patients must have at least one medical condition that qualifies for the program and must have that condition certified by a registered health care practitioner (HCP). After their medical condition is certified, patients have 90 days to submit a complete application to enroll in the program. Patients must also submit payment to cover the annual enrollment fee along with their application materials. Once the application and enrollment fee are submitted, Office of Medical Cannabis (OMC) staff reviews and verifies all submitted materials and can approve the patient for the program. Figure 2.5 depicts the process flow from certification to program approval:

Figure 2.5. Flow chart of enrollment events.



To give current and prospective patients some idea of the time it takes to go from certification to program approval, records from patients in the first program year cohort (n = 1660) were analyzed at different time points: 1) time between certification to program approval, 2) time between certification to enrollment payment, and 3) time between enrollment payment and program approval.

Time from Certification to Program Approval

Just over half of all patients (54.7%) in the cohort (n = 1660) were approved/enrolled in the program within 3 days of having their condition(s) certified. Close to 90% (1484 out of 1660 patients) were enrolled in the program within a month of being certified.

Time from Certification to Annual Enrollment Fee Payment

Records of enrollment fee payments were unavailable for patients who did not make an electronic payment; therefore, calculations of time between certification and enrollment fee payment was restricted to 1579 patients (95.1% of patients in the cohort represented) who paid the enrollment fee electronically. Of these patients, 57.2% of them (n = 903) submitted payment within 1 day of getting their qualifying condition(s) certified by their HCP. More than 90% of patients (n = 1452) submitted payment within one month of certification.

Time from Annual Enrollment Fee Payment and Program Approval

Records of enrollment fee payments were not available for all patients in the cohort; therefore, calculations of time between enrollment fee payment and program approval was restricted to 1579 patients (95.1% of patients in the cohort represented). Of these patients, 72.7% of them (n = 1148) were approved for the program (officially enrolled in the program) within a day of submitting their annual enrollment fees. Close to all patients (99.3%) were enrolled in the program within a month of submitting their annual enrollment fees. The small proportion of patients who do not get approved within a month of their fee submission generally reflects patients who submitted inadequate or incomplete information during the enrollment submission process (meaning that the Office of Medical Cannabis is waiting for additional information to approve them for the program).

From Certification to Program Approval: Conclusions

Just over half of all patients in the cohort were officially enrolled in the program within three days of being certified. Within a week of certification, 70% of patients were enrolled in the program. This suggests that the majority of patients move relatively quickly from certification to enrollment in the program.

When breaking down the process flow between certification and program approval, it typically took longer for patients to move from certification to paying the enrollment fee than it did from their paying the enrollment fee to getting approved. This generally reflects the nature of the process flow going from certification to paying the enrollment fee: after patients are certified, the patient must self-initiate and complete the submission of all application materials along with payment (involves variable amounts of time to gather all materials and to ensure sufficient funds to make fee payment). This is in contrast to the step between enrollment fee payment and getting approved for the program: patient has submitted all materials and payment by this

point and – unless they are directed otherwise by OMC staff – will get approved for the program in the order their materials were received in the queue.

Re-Enrollment

The Minnesota medical cannabis program requires by statute that once a patient becomes certified as having a qualifying condition and enrolled in the program, the patient's enrollment lasts for one year; therefore each year a patient must be re-certified as having at least one qualifying condition and must re-enroll in the program and pay an annual enrollment fee. If a patient is not re-certified as having a qualifying condition and does not re-enroll in the program by the anniversary date of the most recent enrollment, their account is deactivated and they are no longer able to purchase medical cannabis from a cannabis patient center or retain the protections of the program. To investigate the rate at which enrolled patients who approach their expiration dates re-enroll in the program, patients who enrolled in the program during the first program month (including those who were approved early, prior to the program start in July 2015) were examined. A total of 253 patients were enrolled in the first program month; these patients' enrollments expired in July 2016. Re-enrollment activity for these patients was examined six months following expiration of the first enrollment year. Within six months following the expiration of the first year of enrollment, 115 (45%) among these patients re-enrolled in the program. Of the remaining 138 patients who did not re-enroll during this period, 24 patients (17%) died within 18 months of initial enrollment. Additionally, patients can re-enroll at any time following expiration, and some patients who did not re-enroll immediately may do so at a later time.

Most patients who re-enrolled within six months of expiration did so prior to expiration (44%) or within the first month after enrollment expiration (40%). Only 3% of these patients re-enrolled beyond three months post expiration. Timing of re-enrollment for patients who initially enrolled during the first program month are shown in Table 2.8.

Table 2.8. Timing of program re-enrollment for patients enrolled in the first program month.

Time Re-Enrollment Occurred	Patient Count (%)
Prior to Expiration	51 (44%)
1st Month After Expiration	46 (40%)
2nd Month After Expiration	0 (0%)
3rd Month After Expiration	15 (13%)
4th Month After Expiration	1 (1%)
5th Month After Expiration	2 (2%)
6th Month After Expiration	0 (0%)
<i>Total Count of Patients Re-enrolled Within 6 Months of Annual Expiration Date</i>	<i>115</i>

Note: Among the 253 patients who enrolled in the program in July 2015, 115 (45%) re-enrolled within six months of expiration. Percentages are based on a total number of re-enrollments within this period (n=115).

At the time of enrollment expiration, a patient can allow their enrollment to lapse without any action or communication with the Office of Medical Cannabis. Currently OMC does not collect information systematically on why patients chose to either re-enroll or let their current enrollment expire. However, some insight into program discontinuation is available from a Continued Use survey, which asks patients who have not purchased medical cannabis for 60 days whether they have decided to stop the treatment, whether they received any benefits from the treatment, and what their reasons are for either stopping or pausing the treatment. Early results looking at patients who purchased medical cannabis within the first three program months but discontinued purchasing for 60 days showed that 62% (n=10) of patients who indicated they planned to stop using medical cannabis (n=16) found little or no benefit from the treatment. Among 59 patients who indicated they were unsure of whether they would continue or that they intended to continue the treatment, 35 (73%) cited cost as a barrier to continuing. These results do not directly answer the question of why some patients do not re-enroll but give some indication of potential reasons for doing so. (For methodology and preliminary results from the Continued Use survey, see [“Early Results of Office of Medical Cannabis Surveys: May 2016”](#) on the [Office of Medical Cannabis](#) website).

3. Health Care Practitioners Registered in the First Program Year

The Minnesota Medical Cannabis program outlines a set of qualifying medical conditions which make a patient eligible for enrollment in the program. By Minnesota statute, a patient must be certified by a Minnesota-licensed physician, physician assistant (PA), or advanced practice registered nurse (APRN) as having one or more of the qualifying conditions. A Minnesota practitioner with appropriate credentials must first register with the Minnesota Medical Cannabis program before they can certify patients for the program: practitioners complete a short online form with their name and clinic information to register. Office of Medical Cannabis staff verify the provider's entered information and their Drug Enforcement Agency (DEA) license prior to approving the practitioner to certify patients. This chapter will describe the certifying healthcare practitioners who registered in the first program year.

Healthcare Practitioner Count, Age and Gender

From July 2015- June 2016, 577 healthcare practitioners licensed in Minnesota registered in the medical cannabis program, including 473 physicians (82%), 77 APRNs (13%) and 27 PAs (5%). Table 3.1 shows the breakdown of healthcare practitioner (HCP) type, gender and average age, based on publicly available data from the Boards of Medical Practice and Nursing. Physicians registered in the program were predominantly male (72%) and were generally older than registered APRNs and PAs, who were predominantly female (88% and 78%, respectively).

Figure 3.1. Count of registered healthcare practitioners during the first program year.

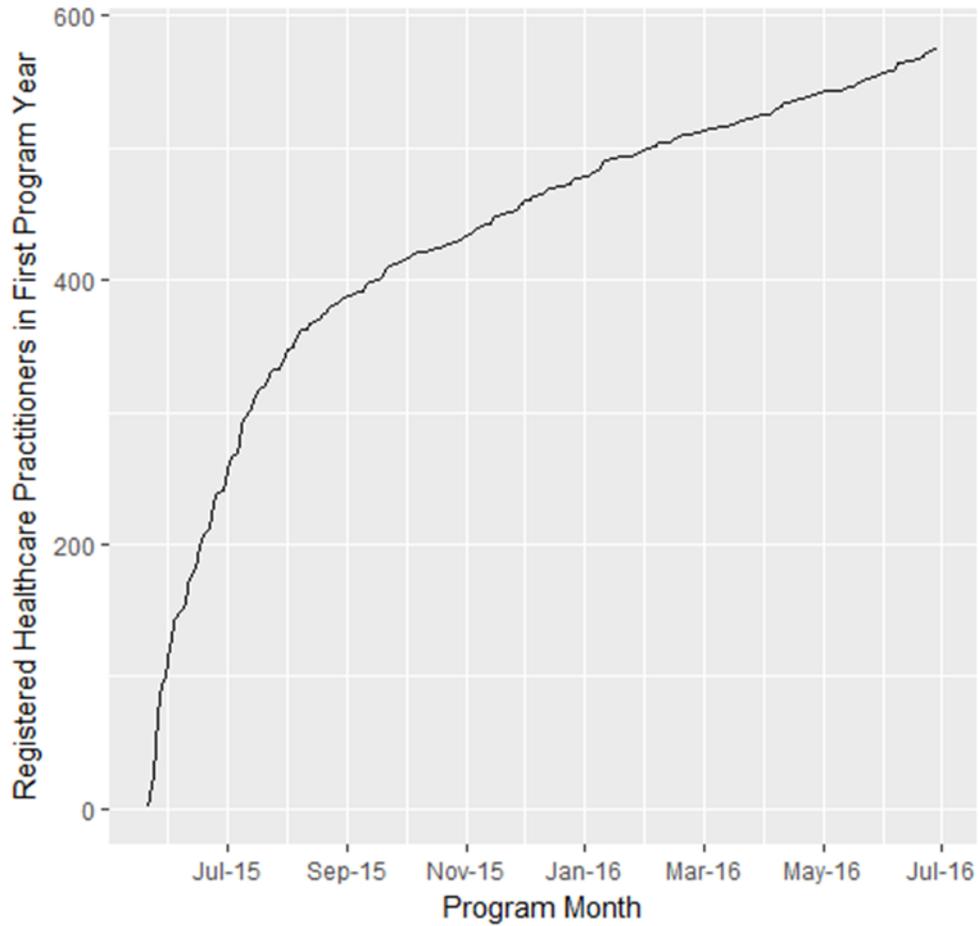


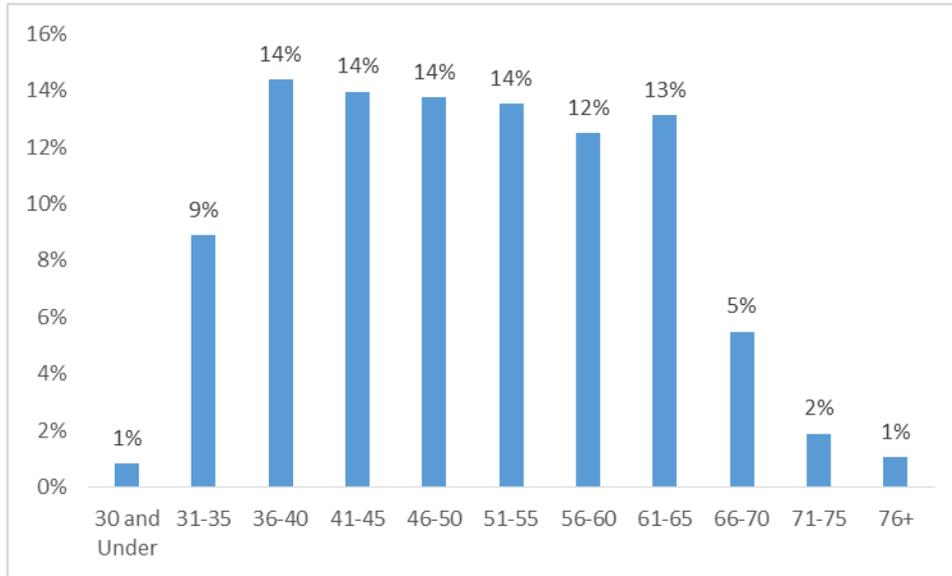
Table 3.1. Healthcare practitioner by type, with gender and average age.

HCP TYPE	N	%	MALE: N (%)	MEAN AGE (SD)
Physician	473	82%	341 (72%)	50.3 (11.3)
APRN	77	13%	9 (12%)	47.0 (9.4)
PA	27	5%	6 (22%)	39.9 (9.5)
Total	577	100%	356 (62%)	49.4 (11.2)

Note: Age data was unavailable for 17 APRNs and three physicians.

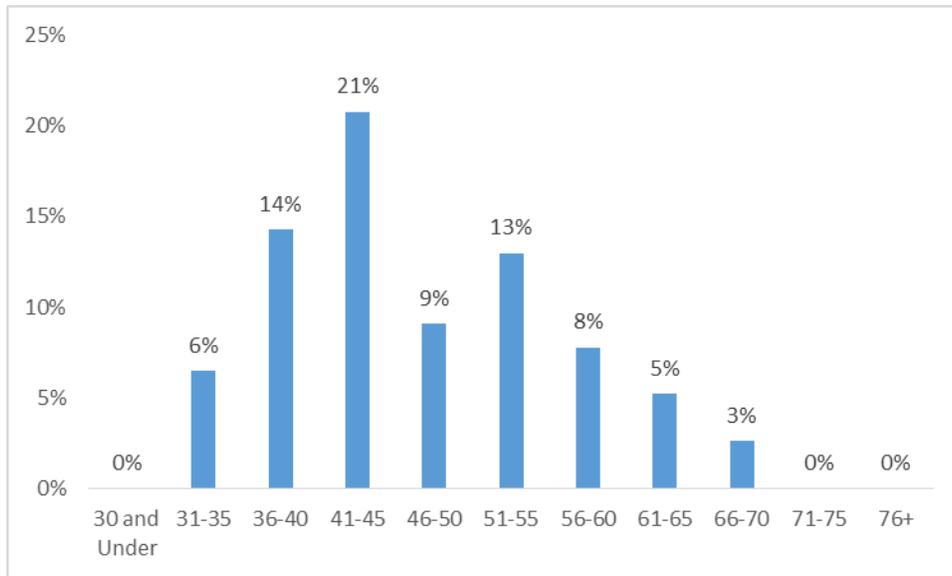
More detailed representations of age distribution among registered physicians, PAs and APRNs are available in Figures 3.2-3.4. Figure 3.2 shows the age distribution in 5 year increments of physicians enrolled in the first program year; most physicians fall between ages 36-65 years (81%) with relatively even distribution of numbers across this range. Figure 3.3 shows the age distribution for APRNs; 51% of APRNs are 50 years or under. Figure 3.4 shows the age distribution for PAs registered in the program; most PAs fall between ages 31-45 (78%).

Figure 3.2. Age distribution of physicians registered in the medical cannabis program (n=473).



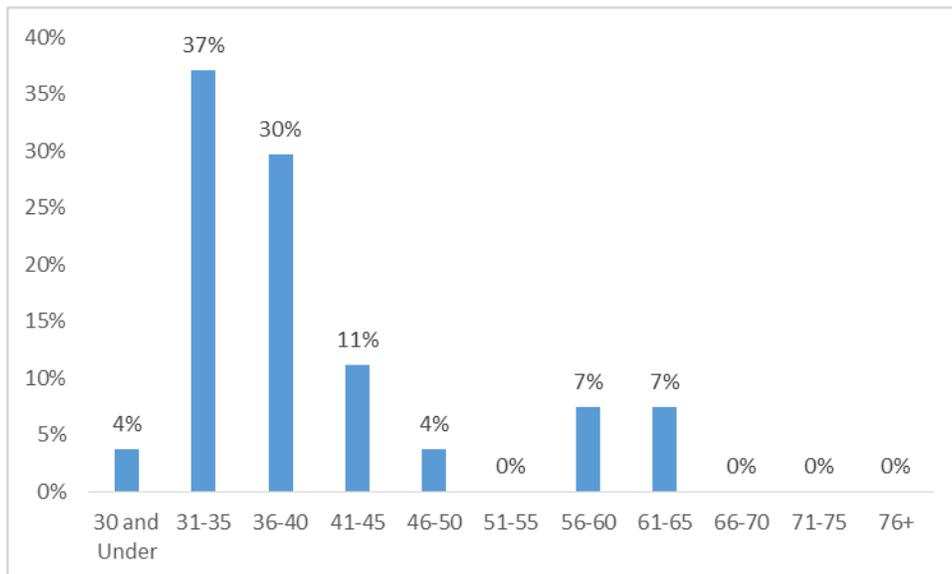
Note: Age data was not publicly available for three physicians registered in the first program year.

Figure 3.3. Age distribution of advanced practice registered nurses registered in the medical cannabis program (n=77).



Note: Age data was not publicly available for 17 APRNs registered in the first program year.

Figure 3.4. Age distribution of physician assistants registered in the medical cannabis program (n=27).



Registered Physician Specialties and Licensures

The Minnesota Board of Medical Practice lists information on Minnesota-licensed physicians and physician assistants. Included is self-reported “Area of Specialty” information indicating a physician’s (or physician assistant’s) certifications from the American Board of Medical Specialties or American Osteopathic Specialty Boards. While physician assistant specialty information is infrequently provided, physicians often list certifications in more than one area of specialty. For example, physicians practicing as oncologists may list certifications in the areas of Internal Medicine, Hematology, and Medical Oncology. A variety of specialties were represented among physicians registered in the first program year, including subspecialties of neurology (neurology with special qualifications in child neurology, clinical neurophysiology, and epilepsy), pediatrics (pediatric hematology-oncology) and internal medicine or family medicine (gastroenterology, geriatric medicine, hospice and palliative medicine, sports medicine, nephrology, and infectious disease). Specialties including ophthalmology, dermatology, radiology and surgery were also represented. In cases where a physician listed an area of specialty and subspecialty, such as Internal Medicine and Gastroenterology, the subspecialty was chosen to represent the physician’s practice (in this case, Gastroenterology). Table 3.2 shows the distribution of physician specialties; each physician is represented only once. Two physicians who are licensed in Minnesota and registered in the program do not have any listed specialties with the Board of Medical Practice; they are therefore excluded from Table 3.2. The most common specialty category for physicians registered in the first program year was primary care (38%), which included internal medicine (13%), family medicine (23%) and pediatrics (2%). Physicians with specialization in oncology (17%) and neurology (14%) were also common.

Table 3.2. Registered physician specialty categories.

Registered Physician Specialties	N (%)
Primary Care	179 (38%)
<i>Internal Medicine</i>	<i>61 (13%)</i>
<i>Family Medicine</i>	<i>109 (23%)</i>
<i>Pediatrics</i>	<i>8 (2%)</i>
Oncology	81 (17%)
Neurology	65 (14%)
Pediatric Specialty	29 (6%)
Hospice/Palliative Medicine	25 (5%)
Physical Medicine and Rehabilitation	21 (4%)
Gastroenterology	11 (2%)
Psychiatry	10 (2%)
Ophthalmology	9 (2%)
Surgery	8 (2%)
Infectious Disease	6 (1%)
Radiology/Radiation Oncology	5 (1%)
Pain Medicine	5 (1%)
Nephrology	3 (1%)
Geriatric Medicine	3 (1%)
Emergency Medicine	2 (0%)
Rheumatology	2 (0%)

Obstetrics and Gynecology	2 (0%)
Sports Medicine	2 (0%)
Anesthesiology	2 (0%)
Dermatology	1 (0%)
Public Health and Preventive Medicine	1 (0%)
Pulmonary Disease	1 (0%)
Sleep Medicine	1 (0%)

Advanced Practice Registered Nurse Licensures

Advanced practice RNs include licensed Clinical Nurse Specialists (CNS), Certified Registered Nurse Anesthetists (CRNA), Certified Nurse-Midwives (CNM) or Certified Nurse Practitioners (CNP). Among the 77 APRNs who registered in the first program year, 75 held CNP certification, 1 held CNS certification, and 1 held both CNP and CNS certifications.

Summary

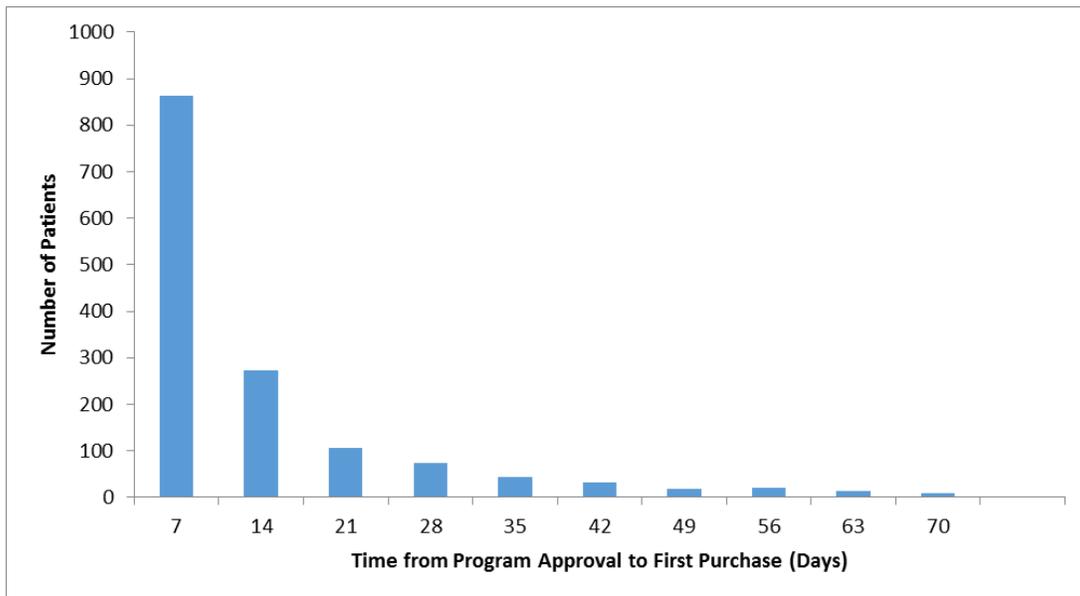
In the first year of the Minnesota Medical Cannabis program, 577 licensed healthcare practitioners registered as certifying providers with the program, predominantly physicians (82%). There were age and gender differences across the HCP types; physicians tended to be older and male; PAs and APRNs tended to be younger and female. Physician licensure information showed that physicians from a diversity of clinical practices are involved in certifying patients for the medical cannabis program, but the majority of these providers are primary care providers or specialties that typically manage patients with the Minnesota program’s qualifying conditions (i.e. severe muscle spasms, seizure disorders, Tourette syndrome and ALS are typically managed by neurologists; cancer is often managed by oncologists).

4. Frequency and Duration of Medical Cannabis Purchases

Time from Program Approval to First Medical Cannabis Purchase

Once a patient is approved for the medical cannabis program, the patient and/or their registered caregiver(s) or parent(s)/legal guardian(s) can visit any of the eight cannabis patient centers and purchase medical cannabis. Figure 4.1 shows the distribution of time from program approval to first medical cannabis purchase for patients enrolled during the first program year who purchased medical cannabis before December 31, 2016 (n=1528). Many patients (n=196; 13%) made a first purchase within one day of program approval; over half (n=864; 57%) made a first purchase within seven days and most patients (n=1137; 74%) made a first purchase within 14 days of program approval.

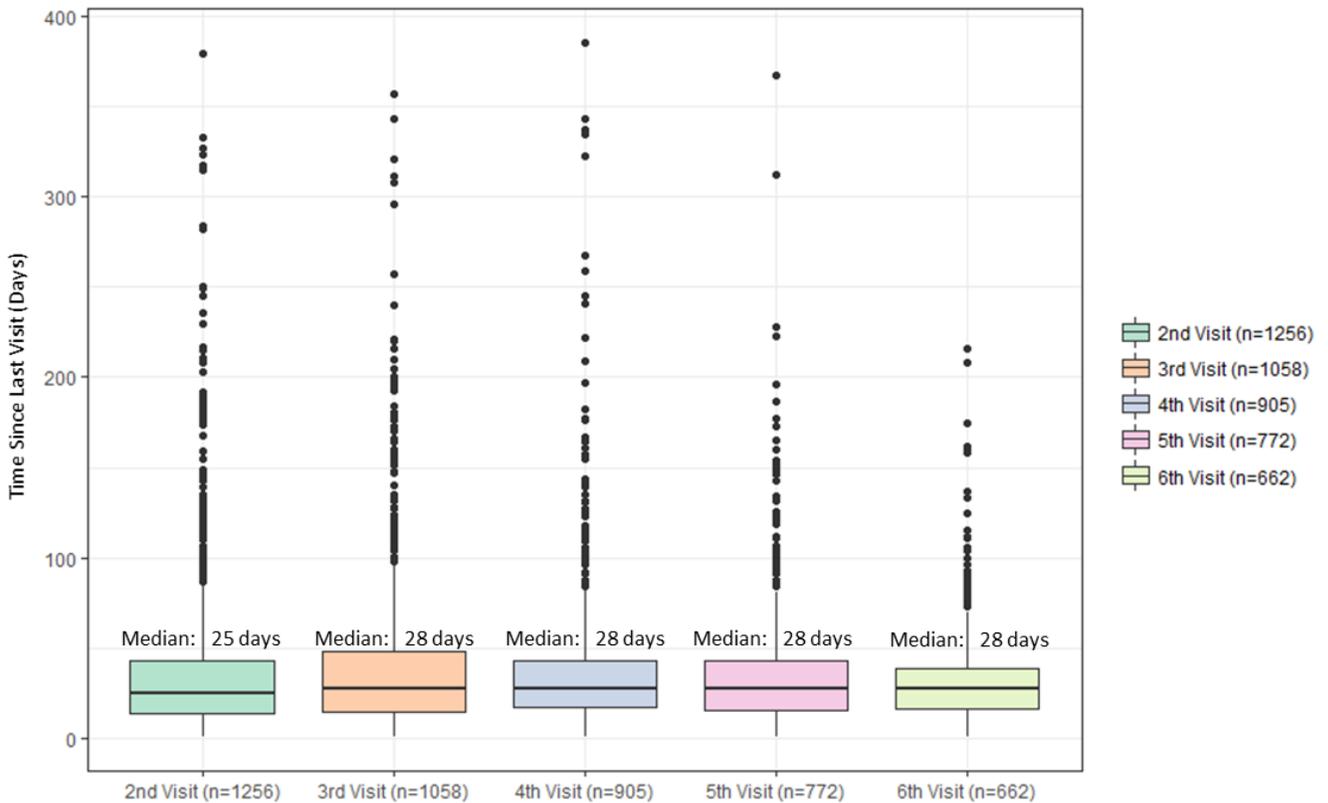
Figure 4.1. Time from patient approval to first medical cannabis purchase.



Time Between Purchases

According to Minnesota statute, patients can purchase up to a 30-day supply of medicine at a cannabis patient center. However, visits to a cannabis patient center vary from 30-day intervals for several reasons. Figure 4.2 shows the intervals between purchases for patients from the one-year cohort with at least two purchases (n=1256). Patients must purchase medical cannabis with cash and many patients report that the medicine's cost is prohibitive; for these reasons, patients may purchase smaller quantities than a month's supply and visit cannabis patient centers more frequently than once a month. On the other hand, many patient responses to the Continued Use Survey (see ["Early Results of Office of Medical Cannabis Surveys: May 2016"](#) on the [Office of Medical Cannabis](#) website) indicated a quantity of medicine intended to be a 30-day supply lasted longer than 30 days, or the patient chose to use the medicine sparingly as a cost-saving measure and therefore the supply lasted longer than anticipated. However, the median times between visits for the first consecutive six visits were close to the expected interval of one month (median time since last visit: 25, 28, 28, 28, and 28 days for the second, third, fourth, fifth and sixth visits, respectively).

Figure 4.2. Time between visits for patients with two or more visits from July 2015-December 2016.



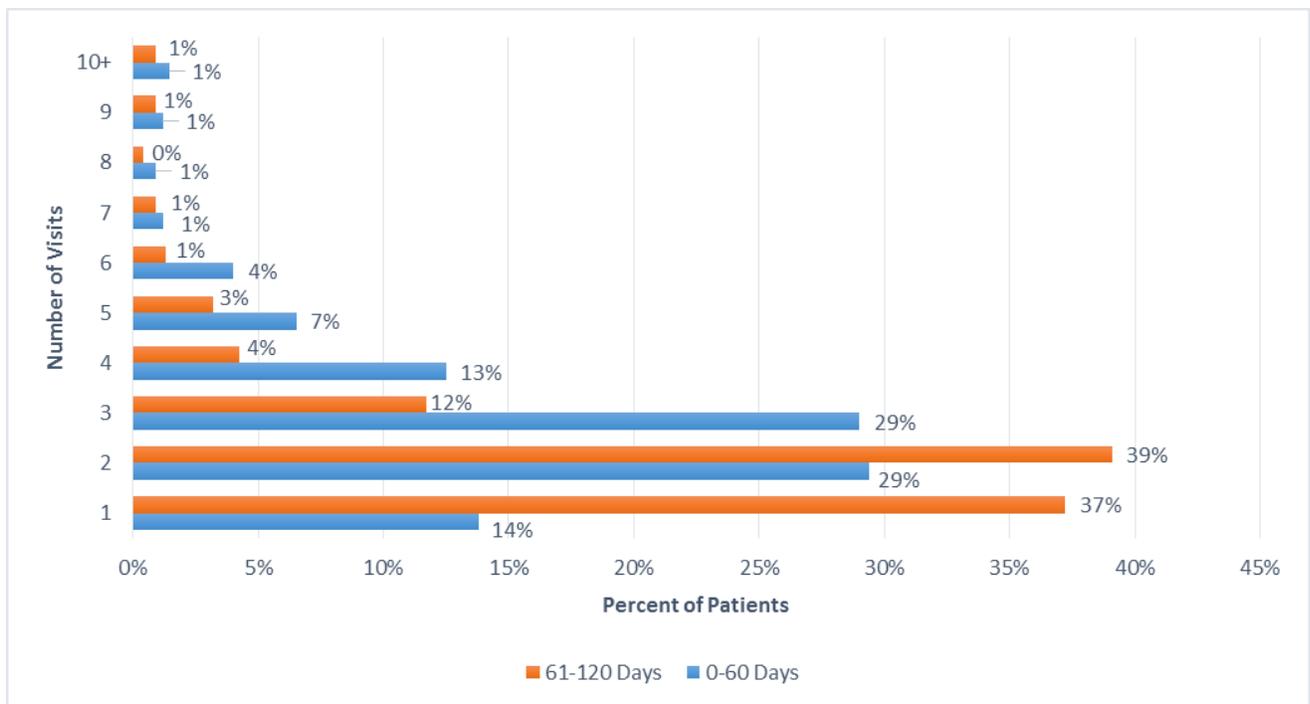
Note on boxplots: upper and lower hinges for each boxplot correspond to the 75th and 25th percentiles of each distribution, respectively. The upper and lower whiskers extend to the highest and lowest values that are within 1.5 x the interquartile range from the upper and lower hinges, respectively. Data beyond the whiskers, plotted as individual points, are outliers.

Purchasing Activity in First Four Months of Program Participation

Patients beginning medical cannabis treatment often try different types of products with varying ratios of THC:CBD and routes of administration to achieve optimal symptom management; therefore patients may be more likely to make more visits to cannabis patient centers at the beginning of treatment and fewer visits in later times once the patient’s regimen had been established. As seen in Figure 4.2, frequency of visits (represented as time between consecutive visits) varies widely across patients. To compare purchasing activity in the first two months versus the second two months of program activity, the number of visits for each patient with continuous enrollment was examined in the first and second 60 days of program activity (day 0 defined as the date of first medical cannabis purchase). Patients who made no

purchases between days 61 and 120 or beyond day 120 were excluded to eliminate patients who had atypical purchasing activity or quit the program during this time window. Figure 4.3 shows the distribution of number of visits per patient which occurred in the first and second 60 days of program activity (n=752). During the first 60 days of program activity, median number of visits was 3 and 543 of 752 patients in this group (72%) made three or fewer purchases. During days 61-120 of program activity, median number of visits was 2 and 662 of 752 patients (88%) made three purchases or less. While the distributions of purchasing activity in the first 60 days and second 60 days is roughly similar, they indicate that purchasing activity is slightly greater during the first 60 days of program activity.

Figure 4.3. Number of visits in first 60 days and second 60 days of program activity, for patients with one or more purchases in both 60 day intervals.

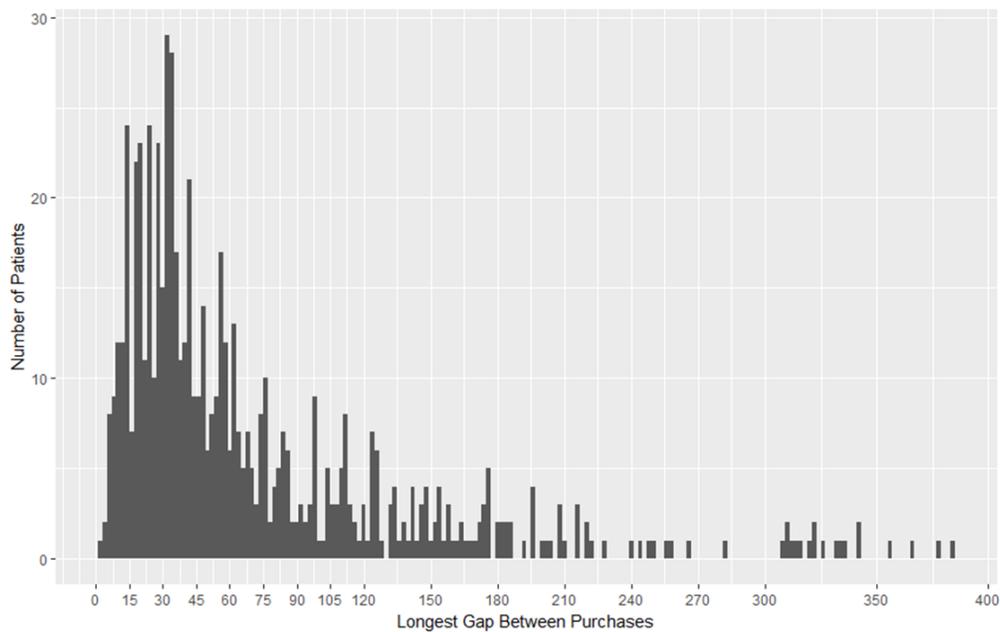


Patients Who Stopped Purchasing Medical Cannabis

Since patients make an annual payment to be enrolled in the medical cannabis program, if they decide at some point during the following year to discontinue medical cannabis treatment, it is unlikely they will request to be withdrawn from the program, as there is no financial incentive to do so. Therefore, to understand discontinuation in the program, a functional definition was created based on purchasing patterns. For each patient in the one year cohort enrolled with a first purchase prior to December 31, 2015 and making at least two purchases before December 31, 2016 (n=669), the longest gap between consecutive purchases from July 2015-December 2016 is shown in Figure 4.4; median longest gap in this group was 47 days. Among these

patients, 546 (82%) had a longest gap between purchases of 120 days or less; 616 (92%) had a longest gap between purchases of 180 days or less. Median longest gap for each patient is significantly longer than median time between visits for patient’s first six visits; this suggests that there may be a great deal of variability within a patient’s inter-visit times. Early patient responses to the Continued Use survey point to factors which may impact purchasing frequency: unexpectedly low rate of product usage, cost-motivated reduction or temporary cessation of product usage, unrelated medical treatment changes which interfered with cannabis usage, or out-of-state travel.

Figure 4.4. Distribution of longest gap between visits per patient, July 2015-December 2016.



Since most patients (92%) enrolled and purchasing within the first six program months who made two or more purchases by December 31, 2016 had no inter-visit gaps longer than 180 days, program discontinuation was defined for this analysis as ceasing purchasing activity for six months or longer during the period included in this analysis (July 2015-December 2016). This definition was applied to all patients enrolled in the first six program months who made at least one purchase (n=774) to find the proportion of patients (regardless of duration enrolled in the program) who did not make any purchases for at least six months, through the end of 2016. Of these 774 patients making at least one medical cannabis purchase, 398 patients (51%) made no purchases for at least six months, as of December 2016. Based on the distribution of longest gaps between purchases in this subset of the one-year cohort, it is likely that this proportion is

a rough estimate of the proportion of patients who quit the program within 18 months after trying medical cannabis.

Using a six month window with no purchases as a surrogate for program discontinuation has limitations. For example, our analysis did not account for duration of enrollment and any effect it may have on purchasing patterns. However, it gives an approximation of patients who abandon medical cannabis treatment and roughly aligns with the re-enrollment rate of 45% in patients enrolled in the first program month (see “Re-Enrollment” in Chapter 2: Description of Patients and Designated Caregivers).

Frequency and Duration of Medical Cannabis Purchases: Conclusions

Most patients make their first medical cannabis purchase within 14 days of program approval. Subsequent purchases often follow a roughly monthly periodicity, with median inter-visit gap at 25 days for the gap between the first and second visit and 28 days for the next four inter-visit gaps. Additionally, patients tend to make purchases slightly more frequently in the first 60 days of program activity compared to the second 60 days of program activity (median number of visits is 3 from 0-60 days and 2 from 61-120 days). Finally, most patients (92%) do not have an inter-visit gap longer than 180 days; using 6 months or more of no purchasing activity as a surrogate for program discontinuation, 51% of patients who enrolled and made a purchase within the first six months of the program ceased purchasing medical cannabis as of December 31, 2016.

5. Medical Cannabis Use Patterns

Medical cannabis purchasing records were extracted from the registry in early March 2017 for patients enrolled in the 1st program year. From this data, all transactions that occurred within a patient's first enrollment year were retained. For those patients whose first enrollment year had not yet ended at the time of data extraction, all purchasing transactions were retained. This resulted in a dataset with the following:

- 10,898 purchasing transactions consisting of:
- 16,238 products within these transactions (37.9% of all purchasing transactions consisted of two or more products), which
- Represented 1529 patients (92.1% of the first program year cohort).

For analytical purposes, all 16,238 product transactions were classified according to the ratio of delta-9-tetrahydrocannabinol (THC) to cannabidiol (CBD) found in the medical cannabis products. Products ranged from containing very high THC to CBD content to those with very high CBD to THC, as well as everything in between (products with relatively balanced amounts of THC and CBD). For definitions on THC:CBD ratio classifications, see Box 5.1.

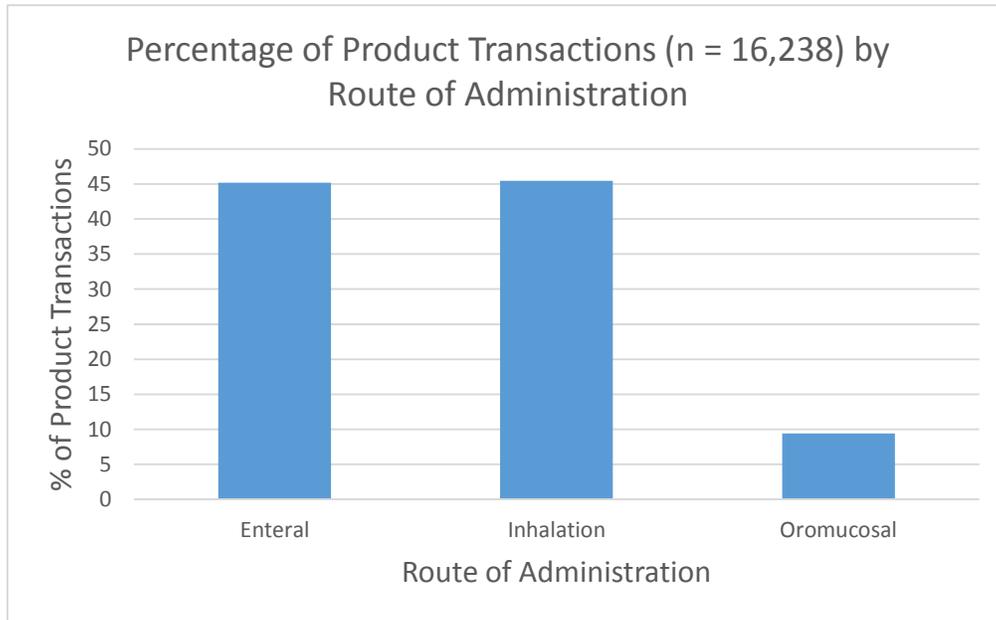
Box 5.1. Definitions to classify medical cannabis products by THC:CBD ratios.

Product Classifications Based on THC to CBD content:

- **Very High THC to CBD** = 100:1 or higher
- **High THC to CBD** = >4:1 up to 99:1
- **Balanced** = 1:1 up to 4:1
- **High CBD to THC** = \geq 1:1 up to 99:1
- **Very High CBD to THC** = 100:1 or higher

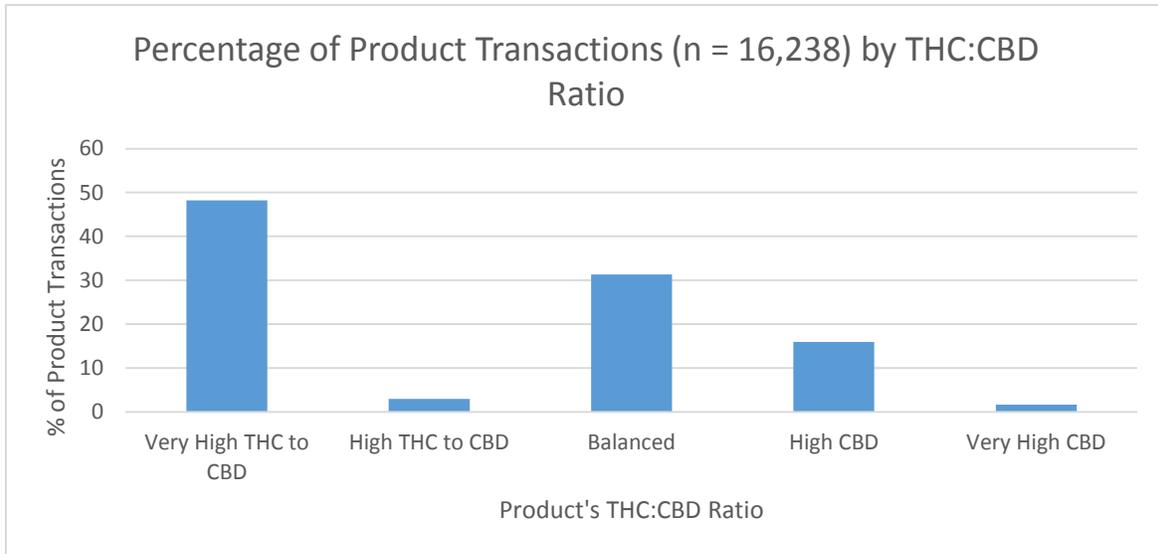
Products purchased for enteral administration (swallowed – includes capsules and oral solutions) and inhalation (vaporized oil) represented the majority of the products purchased (90.6% of all product transactions) with significantly fewer products purchased for oromucosal absorption (oil absorbed through cheek; 9.4% of all product transactions). In fact, products for enteral administration and inhalation were roughly equally purchased by patients, respectively representing 45.2% (n = 7333) and 45.4% (n = 7376) of all products dispensed. See Figure 5.1.

Figure 5.1. Purchasing transactions categorized by the product’s intended route of administration (out of 16,238 products dispensed).



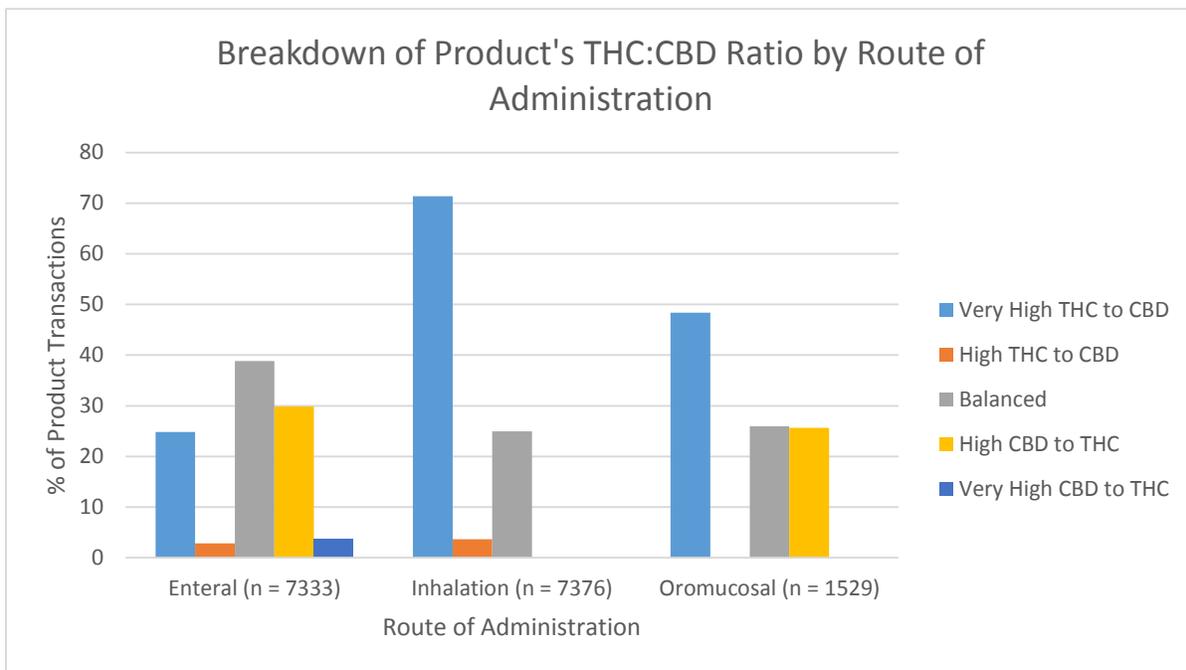
When products were classified by the ratio of THC to CBD present in the product, the following patterns emerged. Firstly, 48.2% of all product transactions were for products with very high THC amounts compared to CBD (hundreds to one). Balanced products (roughly equal amounts of THC to CBD) represented the next biggest group of products purchased, representing 31.3% of products dispensed. This was followed by high CBD to THC products which represented 15.9% of all product transactions. See Figure 5.2.

Figure 5.2. Product transactions represented by the THC to CBD ratio available in the product.



Product transactions were also examined by the products' THC:CBD ratios as a function of their routes of administration (see Figure 5.3). Of all product transactions intended for enteral administration, close to 39% of them were for products with relatively balanced THC:CBD ratios followed by products with high CBD:THC (29.9%) and very high THC:CBD products (24.8%). Product transactions for inhalation predominately had very high THC to CBD (71.4%). Lastly, close to half (48.4%) of all oromucosal product transactions were for very high THC:CBD products, with roughly a quarter each constituting balanced and high CBD to THC products (respectively 26.0% and 25.6%).

Figure 5.3. A percentage breakdown of product transactions by the THC:CBD product ratio types as a function of route of administration.



Most Frequently Purchased Product(s)

Examining purchasing history across all patients is very complex. For example, patients may experiment with different products as they explore what works best for them, and some may establish a pattern of using more than one product. Additionally, those using more than one product do not always purchase all of those products at each purchasing transaction. As a first approach to assessing routine use of products, we report here the product(s) most frequently purchased by each patient. Table 5.1 shows the product(s) that were identified as the most frequently purchased by patients (indicated by “X”), as well as the percentage of patients it represents from the 1529 patients included in this analysis. Additionally, the table displays the average daily THC and CBD dose across patients for the product(s) purchased most frequently based on THC/CBD content information (provided by the medical cannabis manufacturers) as well as pharmacist-entered information regarding the length of time the product supply should last. Omitted from display in Table 5.1 are cases where two or less people had the same combination of most frequently purchased product(s)—this was done for ease of interpretation, as some of those cases seemed to be indicative of a wider range of experimentation across multiple products and/or indicative of patients with a shorter purchasing history.

Table 5.1 shows that roughly 72% of all patients most frequently purchased a single product that falls under 1) a specific THC:CBD ratio and 2) is intended for a particular route of administration (note the rows that have a single “X” in Table 5.1). Roughly a quarter of all patients most frequently purchased a very high THC to CBD product intended for vaporization followed by relatively similar numbers of patients most frequently purchasing a single, balanced-enteral product or a single, high CBD:THC-enteral product (respectively 12.6% and 13.7%). For patients most frequently purchasing two or more products an equal number of times, the most common combination was for an enteral-balanced product and an inhaled-very high THC:CBD product, accounting for 3% of all patients.

While the subsequent portions of this section will be devoted to stratifying routine product use by qualifying condition, the following statement should be made: the method for determining routine product use in this report (most frequently purchased) is relatively simple and, therefore, poses limitations for understanding the complexities in medication usage. Future endeavors will include a further discussion and potential refinement in methodology to better capture medical cannabis use in program participants

Table 5.1. Product(s) most frequently purchased by each patient (out of 1529 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 1529 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
					X										25.4 (389)	83.2 mg / 0.4 mg
			X												13.7 (209)	8.5 mg / 174.2 mg
		X													12.6 (193)	38.8 mg / 29.7 mg
							X								5.8 (88)	39.5 mg / 17.2 mg
X															5.0 (77)	70.8 mg / 0.3 mg
										X					4.3 (66)	39.8 mg / 0.2 mg
		X			X										3.0 (46)	99.2 mg / 47.5 mg
					X		X								2.7 (41)	84.9 mg / 14.0 mg
X					X										2.4 (36)	69.5 mg / 0.4 mg
												X			2.2 (34)	46.3 mg / 33.0 mg
		X					X								2.1 (32)	44.0 mg / 26.5 mg
X		X													1.4 (21)	48.0 mg / 15.0 mg
				X											1.3 (20)	6.9 mg / 1225.3 mg
		X								X					1.2 (19)	82.5 mg / 30.8 mg
					X					X					1.2 (18)	91.3 mg / 0.5 mg
													X		1.2 (18)	2.9 mg / 121.6 mg
X										X					1.0 (15)	46.8 mg / 0.2 mg
X		X					X								0.9 (14)	65.6 mg / 18.2 mg
X		X			X		X								0.7 (11)	164.8 mg / 54.1 mg
X		X			X										0.7 (10)	137.0 mg / 21.9 mg
		X			X		X								0.6 (9)	838.8 mg / 211.5 mg
							X								0.6 (9)	963.5 mg / 56.7 mg
		X	X												0.5 (8)	18.4 mg / 121.9 mg
X					X					X					0.5 (7)	119.6 mg / 0.6 mg
	X														0.5 (7)	873.5 mg / 19.2 mg
		X	X				X								0.4 (6)	37.0 mg / 105.6 mg
			X	X											0.3 (5)	10.9 mg / 539.0 mg
			X		X										0.3 (5)	56.8 mg / 224.2 mg
			X				X								0.3 (5)	66.7 mg / 663.6 mg
					X	X									0.3 (5)	205.7 mg / 8.8 mg
										X		X			0.3 (5)	46.6 mg / 10.4 mg
		X										X			0.3 (4)	63.9 mg / 45.8 mg
			X							X					0.3 (4)	32.3 mg / 78.8 mg

MINNESOTA MEDICAL CANNABIS PROGRAM: PATIENT EXPERIENCES FROM THE FIRST PROGRAM YEAR

Table 5.1 Continued. Product(s) most frequently purchased by each patient (out of 1529 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 1529 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
X		X	X												0.2 (3)	110.4 mg / 125.2 mg
X		X								X					0.2 (3)	54.1 mg / 8.7 mg
X					X		X								0.2 (3)	122.7 mg / 25.1 mg
	X	X			X										0.2 (3)	94.4 mg / 11.3 mg
							X					X			0.2 (3)	52.2 mg / 23.4 mg
							X						X		0.2 (3)	30.5 mg / 133.2 mg
												X	X		0.2 (3)	31.5 mg / 134.4 mg

Severe and Persistent Muscle Spasm Patients

Of the 1529 patients represented in this analysis, 44.3% (677) of them were certified as having Severe and Persistent Muscle Spasms, including those Characteristic of Multiple Sclerosis. Table 5.2 shows the product(s) that were identified as the most frequently purchased by muscle spasm patients (indicated by “X”), as well as the percentage of patients it represents from the 677 patients included in this analysis.

The most frequently purchased product for the majority of patients (70.2%) was a single product with a specific THC:CBD ratio and route of administration. The most common product purchased was a very high THC:CBD-inhaled product (32.3% of all patients) followed by a balanced-enteral and balanced-inhaled product (16.7% and 7.2%, respectively). For patients who purchased multiple products most frequently an equal number of times, the most common combination purchased was for a very high THC:CBD-inhaled product and a balanced-enteral product, accounting for 4.3% of all patients.

Table 5.2. Product(s) most frequently purchased by each muscle spasm patient (out of 677 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 677 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
					X										32.3 (219)	95.2 mg / 0.4 mg
		X													16.7 (113)	37.8 mg / 31.4 mg
							X								7.2 (49)	34.1 mg / 16.9 mg
X															5.3 (36)	69.0 mg / 0.3 mg
		X			X										4.3 (29)	115.7 mg / 64.8 mg
					X	X									4.0 (27)	89.2 mg / 15.0 mg
			X												2.8 (19)	9.9 mg / 190.1 mg
										X					2.8 (19)	41.0 mg / 0.2 mg
		X					X								2.4 (16)	46.3 mg / 27.9 mg
X					X										1.9 (13)	72.9 mg / 0.4 mg
												X			1.9 (13)	19.7 mg / 14.2 mg
X		X													1.5 (10)	57.0 mg / 18.4 mg
X		X			X										1.0 (7)	167.3 mg / 24.2 mg
X		X					X								1.0 (7)	67.2 mg / 18.3 mg
		X								X					1.0 (7)	60.0 mg / 23.8 mg
X		X			X	X									0.9 (6)	219.9 mg / 77.3 mg
		X	X												0.7 (5)	16.8 mg / 102.8 mg
		X			X	X									0.7 (5)	1449.9 mg / 370.4 mg
						X									0.7 (5)	150.9 mg / 8.9 mg
					X					X					0.6 (4)	111.8 mg / 0.6 mg
X										X					0.4 (3)	54.9 mg / 0.2 mg
		X	X				X								0.4 (3)	50.7 mg / 121.2 mg
	X				X										0.3 (2)	170.3 mg / 4.5 mg
			X		X										0.3 (2)	56.3 mg / 90.6 mg
			X				X								0.3 (2)	30.3 mg / 80.0 mg
					X	X									0.3 (2)	184.2 mg / 7.9 mg
										X		X			0.3 (2)	39.7 mg / 15.1 mg
X		X	X												0.3 (2)	38.1 mg / 89.9 mg
X					X					X					0.3 (2)	193.1 mg / 1.0 mg
X		X			X					X					0.3 (2)	107.6 mg / 14.2 mg

Table 5.2 Continued. Product(s) most frequently purchased by each muscle spasm patient (out of 677 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 677 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
	X														0.1 (1)	166.7 mg / 15.7 mg
				X											0.1 (1)	1.0 mg / 182.6 mg
X							X								0.1 (1)	131.4 mg / 18.2 mg
		X		X											0.1 (1)	10.1 mg / 205.5 mg
		X					X								0.1 (1)	80.7 mg / 24.3 mg
		X										X			0.1 (1)	37.4 mg / 37.4 mg
		X											X		0.1 (1)	12.8 mg / 153.4 mg
			X							X					0.1 (1)	16.2 mg / 40.0 mg
			X									X			0.1 (1)	153.9 mg / 919.7 mg
			X										X		0.1 (1)	33.9 mg / 644.0 mg
					X								X		0.1 (1)	88.5 mg / 99.2 mg
							X					X			0.1 (1)	59.0 mg / 41.0 mg
							X						X		0.1 (1)	34.2 mg / 67.2 mg
												X	X		0.1 (1)	39.7 mg / 146.9 mg
X	X	X													0.1 (1)	65.8 mg / 8.0 mg
X	X			X											0.1 (1)	106.1 mg / 201.4 mg
X	X				X										0.1 (1)	111.3 mg / 6.1 mg
X			X		X										0.1 (1)	113.8 mg / 47.7 mg
X					X		X								0.1 (1)	118.8 mg / 36.9 mg
	X				X		X								0.1 (1)	146.1 mg / 18.2 mg
		X	X							X					0.1 (1)	42.3 mg / 113.4 mg
		X	X									X			0.1 (1)	107.4 mg / 108.7 mg
		X			X					X					0.1 (1)	138.5 mg / 43.4 mg
		X			X							X			0.1 (1)	86.4 mg / 44.6 mg
		X					X			X					0.1 (1)	76.5 mg / 32.6 mg
		X								X		X			0.1 (1)	81.1 mg / 51.2 mg
			X	X			X								0.1 (1)	34.7 mg / 302.1 mg
			X		X		X								0.1 (1)	91.7 mg / 742.3 mg
					X		X			X					0.1 (1)	314.3 mg / 25.7 mg
					X		X					X			0.1 (1)	232.5 mg / 127.7 mg

Table 5.2 Continued. Product(s) most frequently purchased by each muscle spasm patient (out of 677 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 677 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
					X		X						X		0.1 (1)	117.1 mg / 112.0 mg
					X					X			X		0.1 (1)	88.3 mg / 47.9 mg
X		X	X				X								0.1 (1)	44.7 mg / 117.0 mg
	X	X			X		X								0.1 (1)	121.6 mg / 31.4 mg
		X	X		X		X								0.1 (1)	70.4 mg / 111.2 mg
		X	X				X					X			0.1 (1)	53.1 mg / 129.1 mg
		X			X		X			X					0.1 (1)	138.2 mg / 21.4 mg
		X				X	X					X			0.1 (1)	258.3 mg / 98.3 mg
			X	X	X					X					0.1 (1)	692.0 mg / 248.8 mg
X		X	X	X			X								0.1 (1)	86.0 mg / 6117.0 mg
X		X			X		X			X					0.1 (1)	135.6 mg / 10.6 mg
		X	X				X			X		X			0.1 (1)	65.8 mg / 69.9 mg
X		X	X	X	X		X								0.1 (1)	139.1 mg / 304.6 mg
X		X			X	X	X			X					0.1 (1)	303.9 mg / 27.8 mg
		X	X		X	X						X	X		0.1 (1)	189.7 mg / 130.6 mg
		X	X		X		X			X		X			0.1 (1)	161.6 mg / 848.6 mg

Cancer Patients

Of the 1529 patients represented in this analysis, 26.6% (406) of them were certified for Cancer. Table 5.3 shows the product(s) that were identified as the most frequently purchased by cancer patients (indicated by “X”), as well as the percentage of patients it represents from the 406 patients included in this analysis.

The majority of patients (61.6%) most frequently purchased a single product with a specific THC:CBD ratio and route of administration. Most commonly purchased products were a very high THC:CBD-inhaled product (23.9% of all patients) followed by a balanced-enteral and very high THC:CBD-oral mucosal product (10.3% and 9.6%, respectively). For patients who purchased multiple products most frequently an equal number of times, the most common combination purchased was for a very high THC:CBD product – one for enteral administration and one for inhalation (accounted for 5.4% of all patients).

Table 5.3. Product(s) most frequently purchased by each cancer patient (out of 406 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 406 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
					X										23.9 (97)	81.4 mg / 0.4 mg
		X													10.3 (42)	46.4 mg / 28.4 mg
										X					9.6 (39)	37.3 mg / 0.2 mg
X															5.9 (24)	108.0 mg / 0.5 mg
X					X										5.4 (22)	62.9 mg / 0.4 mg
							X								3.7 (15)	69.2 mg / 22.6 mg
					X					X					3.2 (13)	87.0 mg / 0.4 mg
		X					X								3.0 (12)	37.7 mg / 21.9 mg
												X			2.7 (11)	58.5 mg / 54.2 mg
		X			X										2.7 (11)	70.6 mg / 17.3 mg
			X												2.5 (10)	9.6 mg / 239.3 mg
X										X					2.2 (9)	45.5 mg / 0.2 mg
		X								X					2.2 (9)	111.8 mg / 39.0 mg
					X		X								1.7 (7)	68.7 mg / 13.7 mg
X		X					X								1.7 (7)	82.8 mg / 22.8 mg
				X											1.5 (6)	3.8 mg / 666.5 mg
X		X													1.5 (6)	47.6 mg / 9.5 mg
X					X					X					1.2 (5)	90.3 mg / 0.5 mg
	X														1.0 (4)	28.6 mg / 5.4 mg
X		X			X		X								1.0 (4)	102.0 mg / 25.3 mg
		X										X			0.7 (3)	72.7 mg / 48.6 mg
										X		X			0.7 (3)	51.2 mg / 7.2 mg
X		X			X										0.7 (3)	64.4 mg / 11.3 mg
X		X								X					0.7 (3)	54.1 mg / 8.7 mg
	X	X			X										0.7 (3)	94.4 mg / 11.3 mg
		X	X				X								0.7 (3)	24.2 mg / 92.5 mg
		X			X		X								0.7 (3)	80.9 mg / 13.3 mg
						X									0.5 (2)	3812.7 mg / 224.3 mg
		X	X												0.5 (2)	20.1 mg / 200.4 mg
			X							X					0.5 (2)	43.0 mg / 97.6 mg
					X	X									0.5 (2)	227.9 mg / 10.4 mg
							X					X			0.5 (2)	48.8 mg / 14.5 mg

Table 5.3 Continued. Product(s) most frequently purchased by each cancer patient (out of 406 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 406 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
													X		0.2 (1)	3.4 mg / 64.8 mg
X			X												0.2 (1)	33.1 mg / 150.1 mg
X												X			0.2 (1)	18.7 mg / 8.8 mg
	X	X													0.2 (1)	181.3 mg / 35.6 mg
	X		X												0.2 (1)	282.1 mg / 525.9 mg
			X		X										0.2 (1)	47.6 mg / 150.2 mg
					X							X			0.2 (1)	97.9 mg / 31.4 mg
					X								X		0.2 (1)	60.8 mg / 117.1 mg
												X	X		0.2 (1)	32.7 mg / 135.4 mg
X	X			X											0.2 (1)	106.1 mg / 201.4 mg
X		X	X												0.2 (1)	13.0 mg / 49.5 mg
X					X		X								0.2 (1)	185.0 mg / 20.5 mg
X					X							X			0.2 (1)	94.5 mg / 24.7 mg
		X			X					X					0.2 (1)	125.6 mg / 50.4 mg
					X		X					X			0.2 (1)	232.5 mg / 127.7 mg
X		X			X	X									0.2 (1)	427.4 mg / 64.7 mg
			X	X	X					X					0.2 (1)	692.0 mg / 248.8 mg
X	X	X	X		X										0.2 (1)	278.3 mg / 302.9 mg
X		X	X		X					X					0.2 (1)	135.4 mg / 296.4 mg
		X	X	X	X		X								0.2 (1)	184.5 mg / 237.7 mg
		X			X		X			X		X			0.2 (1)	128.8 mg / 16.4 mg
		X			X		X					X	X		0.2 (1)	154.6 mg / 139.8 mg

Seizure Patients

Of the 1529 patients represented in this analysis, 19.8% (303) of them were certified for Seizures, including those Characteristic of Epilepsy. Table 5.4 shows the product(s) that were identified as the most frequently purchased by seizure patients (indicated by “X”), as well as the percentage of patients it represents from the 303 patients included in this analysis.

89.1% of all patients most frequently purchased a single product with a specific THC:CBD ratio and route of administration. Most commonly used products were a high CBD:THC-enteral product (59.7% of all patients) followed by a very high THC:CBD-inhaled product and high CBD:THC-oral mucosal product (7.9% and 5.0%, respectively).

Table 5.4. Product(s) most frequently purchased by each seizure patient (out of 303), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 303 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
			X												59.7 (181)	8.3 mg / 170.6 mg
					X										7.9 (24)	75.2 mg / 0.4 mg
													X		5.0 (15)	2.7 mg / 130.4 mg
		X													4.6 (14)	31.1 mg / 24.8 mg
				X											4.3 (13)	7.9 mg / 1394.4 mg
							X								3.6 (11)	36.3 mg / 14.7 mg
												X			2.0 (6)	96.7 mg / 43.3 mg
			X	X											1.7 (5)	10.9 mg / 539.0 mg
X															1.3 (4)	7.8 mg / 0.0 mg
			X				X								1.3 (4)	72.7 mg / 815.1 mg
X		X													0.7 (2)	46.5 mg / 16.6 mg
		X	X												0.7 (2)	22.1 mg / 64.1 mg
		X					X								0.7 (2)	56.7 mg / 46.0 mg
					X		X								0.7 (2)	151.4 mg / 27.6 mg
							X							X	0.7 (2)	32.7 mg / 89.4 mg
X	X	X	X		X										0.3 (1)	278.3 mg / 302.9 mg
X		X	X												0.3 (1)	63.2 mg / 130.4 mg
X		X			X										0.3 (1)	55.3 mg / 3.2 mg
X		X					X								0.3 (1)	36.1 mg / 9.7 mg
X					X		X								0.3 (1)	64.3 mg / 17.7 mg
		X		X											0.3 (1)	10.1 mg / 205.5 mg
		X												X	0.3 (1)	10.0 mg / 100.0 mg
			X	X										X	0.3 (1)	16.5 mg / 492.9 mg
			X		X										0.3 (1)	75.2 mg / 723.6 mg
			X											X	0.3 (1)	33.9 mg / 644.0 mg
				X			X								0.3 (1)	19.0 mg / 217.9 mg
					X	X									0.3 (1)	204.3 mg / 7.3 mg
					X									X	0.3 (1)	88.5 mg / 99.2 mg
						X									0.3 (1)	170.0 mg / 10.0 mg
										X					0.3 (1)	18.0 mg / 0.1 mg
												X	X		0.3 (1)	39.7 mg / 146.9 mg

Crohn's Disease Patients

Of the 1529 patients represented in this analysis, 6.7% (103) of them were certified for Crohn's Disease. Table 5.5 shows the product(s) that were identified as the most frequently purchased by Crohn's patients (indicated by "X"), as well as the percentage of patients it represents from the 103 patients included in this analysis.

71.8% of all patients most frequently purchased a single product with a specific THC:CBD ratio and route of administration. Most commonly used products were a very high THC:CBD-inhaled product (28.2% of all patients) followed by a balanced-enteral and balanced-inhaled product (16.5% and 8.7%, respectively). For patients who purchased multiple products most frequently an equal number of times, the most common combination identified was for a balanced-enteral product and a very high THC:CBD-inhaled product, accounting for 4.9% of all patients.

Table 5.5. Product(s) most frequently purchased by each Crohn’s Disease patient (out of 103 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 103 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
					X										28.2 (29)	70.0 mg / 0.4 mg
		X													16.5 (17)	31.9 mg / 31.5 mg
							X								8.7 (9)	28.5 mg / 12.5 mg
			X												5.8 (6)	15.6 mg / 297.4 mg
		X			X										4.9 (5)	68.9 mg / 16.9 mg
										X					3.9 (4)	35.8 mg / 0.2 mg
						X									2.9 (3)	153.8 mg / 9.0 mg
X					X										2.9 (3)	81.9 mg / 0.6 mg
X															1.9 (2)	15.3 mg / 0.0 mg
												X			1.9 (2)	21.3 mg / 14.5 mg
													X		1.9 (2)	4.4 mg / 83.7 mg
X		X													1.9 (2)	27.8 mg / 13.2 mg
		X					X								1.9 (2)	42.5 mg / 27.9 mg
					X		X								1.9 (2)	68.5 mg / 7.3 mg
		X								X					1.0 (1)	31.2 mg / 15.1 mg
			X		X										1.0 (1)	48.9 mg / 65.8 mg
					X					X					1.0 (1)	65.3 mg / 0.4 mg
X		X			X										1.0 (1)	64.6 mg / 3.3 mg
X										X		X			1.0 (1)	80.0 mg / 25.8 mg
	X				X		X								1.0 (1)	146.1 mg / 18.2 mg
		X	X				X								1.0 (1)	27.5 mg / 57.5 mg
		X			X		X								1.0 (1)	57.0 mg / 11.6 mg
		X					X					X			1.0 (1)	137.5 mg / 87.5 mg
					X		X					X			1.0 (1)	112.1 mg / 35.9 mg
	X	X	X		X										1.0 (1)	112.6 mg / 47.1 mg
		X	X		X		X								1.0 (1)	97.8 mg / 109.5 mg
		X				X	X					X			1.0 (1)	258.3 mg / 98.3 mg
X		X	X	X			X								1.0 (1)	86.0 mg / 6117.0 mg
X		X			X		X			X		X			1.0 (1)	299.4 mg / 152.0 mg

Terminal Illness Patients

Of the 1529 patients represented in this analysis, 5.4% (82) of them were certified for Terminal Illness. Table 5.6 shows the product(s) that were identified as the most frequently purchased by terminal illness patients (indicated by “X”), as well as the percentage of patients it represents from the 82 patients included in this analysis.

68.3% of all patients most frequently purchased a single product with a specific THC:CBD ratio and route of administration. Most commonly used products were a very high THC:CBD-inhaled product (26.8% of all patients) followed by a balanced-enteral and balanced-orumucosal product (both respectively accounting for 8.5% of all patients). For patients who purchased multiple products most frequently an equal number of times, the most common combination identified was for a very high THC:CBD product – one for enteral administration and the other for oromucosal absorption (accounted for 3.7% of all patients).

Table 5.6. Product(s) most frequently purchased by each terminal illness patient (out of 82 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 82 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
					X										26.8 (22)	62.7 mg / 0.4 mg
		X													8.5 (7)	18.9 mg / 18.9 mg
												X			8.5 (7)	24.5 mg / 20.0 mg
										X					7.3 (6)	36.5 mg / 0.1 mg
X															6.1 (5)	17.2 mg / 0.0 mg
			X												6.1 (5)	9.8 mg / 188.2 mg
X										X					3.7 (3)	46.1 mg / 0.1 mg
		X					X								3.7 (3)	47.5 mg / 28.2 mg
								X							2.4 (2)	3812.7 mg / 224.3 mg
X					X										2.4 (2)	57.5 mg / 0.4 mg
		X			X										2.4 (2)	43.0 mg / 2.9 mg
					X					X					2.4 (2)	123.3 mg / 0.5 mg
X		X					X								2.4 (2)	104.5 mg / 25.7 mg
				X											1.2 (1)	5.2 mg / 925.0 mg
							X								1.2 (1)	36.4 mg / 9.1 mg
X		X													1.2 (1)	10.0 mg / 5.0 mg
	X	X													1.2 (1)	37.5 mg / 8.1 mg
		X	X												1.2 (1)	30.6 mg / 293.4 mg
					X		X								1.2 (1)	23.9 mg / 8.8 mg
					X								X		1.2 (1)	60.8 mg / 117.1 mg
							X			X					1.2 (1)	108.5 mg / 11.1 mg
X		X			X										1.2 (1)	66.0 mg / 20.3 mg
X					X					X					1.2 (1)	79.6 mg / 0.4 mg
		X			X		X								1.2 (1)	98.0 mg / 17.9 mg
			X	X	X					X					1.2 (1)	692.0 mg / 248.8 mg
X		X	X		X					X					1.2 (1)	135.4 mg / 296.4 mg
		X			X		X			X		X			1.2 (1)	128.8 mg / 16.4 mg

HIV/AIDS Patients

Of the 1529 patients represented in this analysis, 3.2% (49) of them were certified for Human Immunodeficiency Virus and/or Acquired Immune Deficiency Syndrome (HIV/AIDS). Table 5.7 shows the product(s) that were identified as the most frequently purchased by HIV/AIDS patients (indicated by “X”), as well as the percentage of patients it represents from the 49 patients included in this analysis.

75.5% of all patients most frequently purchased a single product with a specific THC:CBD ratio and route of administration. Most commonly used products were a very high THC:CBD-inhaled product (51.0% of all patients) followed by a balanced-enteral product (12.2% of patients). For patients who purchased multiple products most frequently an equal number of times, the most common combination identified was for two inhaled products – one of a very high THC:CBD ratio and the other a balanced THC:CBD ratio (accounted for 10.2% of all patients).

Table 5.7. Product(s) most frequently purchased by each HIV/AIDS patient (out of 49 patients), along with average daily THC/CBD dose (mg).

Enteral			Inhalation			Oromucosal				
Very High THC to CBD	High THC to CBD	Balanced	Very High THC to CBD	High THC to CBD	Balanced	Very High THC to CBD	High THC to CBD	Balanced	% of Patients out of 49 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
			X						51.0 (25)	93.4 mg / 0.6 mg
		X							12.2 (6)	45.4 mg / 35.9 mg
			X		X				10.2 (5)	76.8 mg / 13.7 mg
X									6.1 (3)	13.4 mg / 0.1 mg
					X				6.1 (3)	30.0 mg / 18.7 mg
		X	X						4.1 (2)	61.3 mg / 16.1 mg
X		X							2.0 (1)	20.0 mg / 15.0 mg
X						X			2.0 (1)	38.4 mg / 0.1 mg
		X			X				2.0 (1)	70.0 mg / 40.0 mg
		X				X			2.0 (1)	53.3 mg / 20.1 mg
			X	X					2.0 (1)	135.0 mg / 5.3 mg

Tourette Syndrome Patients

Of the 1529 patients represented in this analysis, 1.9% (29) of them were certified for Tourette Syndrome. Table 5.8 shows the product(s) that were identified as the most frequently purchased by Tourette Syndrome patients (indicated by “X”), as well as the percentage of patients it represents from the 29 patients included in this analysis.

93.1% of all patients most frequently purchased a single product with a specific THC:CBD ratio and route of administration. Most commonly used products were a balanced-enteral product (20.7% of all patients) followed by a very high THC:CBD-inhaled product and a very high THC:CBD-oral mucosal product (respectively at 20.7% and 13.8% of all patients).

Table 5.8. Product(s) most frequently purchased by each Tourette Syndrome patient (out of 29 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					% of Patients out of 29 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
		X													20.7 (6)	37.4 mg / 20.3 mg
					X										20.7 (6)	78.4 mg / 0.3 mg
										X					13.8 (4)	52.0 mg / 0.2 mg
X															10.3 (3)	21.2 mg / 0.1 mg
							X								10.3 (3)	51.8 mg / 20.1 mg
			X												6.9 (2)	33.4 mg / 633.7 mg
X		X			X		X								3.4 (1)	85.0 mg / 30.3 mg
	X									X					3.4 (1)	178.6 mg / 10.0 mg
	X														3.4 (1)	5812.5 mg / 93.0 mg
				X											3.4 (1)	13.4 mg / 2378.6 mg
												X			3.4 (1)	24.2 mg / 24.2 mg

Glaucoma Patients

Of the 1529 patients represented in this analysis, 1.5% (23) of them were certified for Glaucoma. Table 5.9 shows the product(s) that were identified as the most frequently purchased by glaucoma patients (indicated by “X”), as well as the percentage of patients it represents from the 23 patients included in this analysis.

56.5% of all patients most frequently purchased a single product with a specific THC:CBD ratio and route of administration. Most commonly used products were a very high THC:CBD-inhaled product (21.7% of all patients) followed by a very high THC:CBD-enteral product and a balanced-enteral product (respectively at 17.4% and 13.0% of all patients).

Table 5.9. Product(s) most frequently purchased by each glaucoma patient (out of 23 patients), along with average daily THC/CBD dose (mg).

Enteral			Inhalation			Oromucosal			% of Patients out of 23 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	Balanced	High CBD to THC	Very High THC to CBD	Balanced	High CBD to THC	Very High THC to CBD	Balanced	High CBD to THC		
			X						21.7 (5)	60.1 mg / 0.4 mg
X									17.4 (4)	54.5 mg / 0.3 mg
	X								13.0 (3)	7.1 mg / 3.2 mg
X	X								8.7 (2)	111.8 mg / 21.9 mg
			X	X					8.7 (2)	99.2 mg / 22.6 mg
X	X	X							4.3 (1)	255.0 mg / 195.8 mg
X						X	X		4.3 (1)	71.1 mg / 31.3 mg
X						X			4.3 (1)	61.7 mg / 0.3 mg
	X	X				X			4.3 (1)	42.3 mg / 113.4 mg
	X			X					4.3 (1)	32.0 mg / 8.0 mg
			X	X		X			4.3 (1)	115.9 mg / 31.6 mg
				X					4.3 (1)	40.0 mg / 10.0 mg

ALS Patients

Of the 1529 patients represented in this analysis, 1.4% (21) of them were certified for Amyotrophic Lateral Sclerosis (ALS). Table 5.10 shows the product(s) that were identified as the most frequently purchased by ALS patients (indicated by “X”), as well as the percentage of patients it represents from the 21 patients included in this analysis.

57.1% of all patients most frequently purchased a single product with a specific THC:CBD ratio and route of administration. Most commonly used product was a very high THC:CBD-inhaled product (14.3% of all patients).

Table 5.10. Product(s) most frequently purchased by each ALS patient (out of 21 patients), along with average daily THC/CBD dose (mg).

Enteral				Inhalation				Oromucosal				% of Patients out of 21 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC		
				X								14.3 (3)	44.8 mg / 0.3 mg
		X						X				9.5 (2)	54.9 mg / 26.6 mg
		X										9.5 (2)	16.1 mg / 7.5 mg
						X						9.5 (2)	25.6 mg / 18.1 mg
								X				9.5 (2)	29.8 mg / 0.1 mg
X								X				4.8 (1)	40.0 mg / 0.1 mg
X												4.8 (1)	16.0 mg / 0.0 mg
	X	X		X	X	X						4.8 (1)	205.5 mg / 24.4 mg
	X											4.8 (1)	20.8 mg / 3.9 mg
		X						X		X		4.8 (1)	81.1 mg / 51.2 mg
			X					X				4.8 (1)	27.1 mg / 80.1 mg
				X						X		4.8 (1)	101.2 mg / 8.7 mg
						X					X	4.8 (1)	26.1 mg / 220.8 mg
										X	X	4.8 (1)	22.2 mg / 120.8 mg
										X		4.8 (1)	28.4 mg / 28.4 mg

Medical Cannabis Use Patterns: Conclusions

To establish medication use patterns in program participants, a total of 16,238 product transactions were analyzed from 1529 patients in the 1st program year cohort. When product transactions were examined by each product's intended route of administration and THC:CBD content, the following patterns emerged. Firstly, roughly 90% of all products were purchased for enteral administration (through mouth via capsules or oral solutions) and inhalation (vaporized oil). Secondly, approximately 50% of all product transactions were for products very high in THC relative to CBD followed by balanced THC:CBD products (~30%) and high CBD:THC products (~15%). Very high THC:CBD products were most commonly purchased for inhalation or oromucosal absorption, while balanced and high CBD:THC products were most commonly used for enteral administration.

For this report, the most frequently purchased product(s) were identified for each patient as one method for understanding routine purchasing patterns. 72.5% of all patients most frequently purchased one type of product, with the most frequently purchased single product being a very high THC:CBD-inhaled product followed by a high CBD:THC-enteral and balanced-enteral product. For specific differences in the most frequently purchased products among qualifying conditions, the reader is encouraged to refer back to those specific sections.

6. Benefits

Summary

Information on patient benefits comes from the Patient Self-Evaluation (PSE) completed by patients prior to each medical cannabis purchase and from patient and health care practitioner surveys. Results of analysis of PSE and survey data indicate perceptions of a high degree of benefit for most patients.

Patients responded to a survey question asking them how much benefit they believe they received from using medical cannabis on a scale from 1 (no benefit) to 7 (great deal of benefit). Across all patients 64% indicated a benefit rating of 6 or 7 and this degree of benefit was indicated by at least half of the patients with each medical condition (see Table 6.1). A small but important proportion of patients indicated little or no benefit: 9% gave a rating of 1, 2, or 3. When patients were asked what the most important benefit was for them, two-thirds indicated a reduction in symptoms directly related to their qualifying medical condition and most of the remainder indicated more general quality of life benefits.

An important part of this report is the verbatim comments written by patients, and the reader is encouraged to review these comments in *Appendix A: Patient-Reported Benefits from Surveys*. Examples of these comments include:

- “Almost all muscle spasm and pain associated with spasms are gone. I used to have constant nerve triggered pain that is minimal now. Results were almost immediate. I am sleeping way better now also.”
- “[NAME] has passed away. I am her daughter and was her care giver. She was open to trying medical cannabis and we got the liquid form. It was a saving grace. She was in a lot of pain and when prescribed medications did NOT work – we started this and it kept her calm and relaxed. I am very thankful that we were able to have this option available. It helped to make her last months more bearable and truly it would have been miserable without it.”
- “I am getting enough sleep for the first time since about 2011. My absence seizures have gone from 3-4 a day to almost 0. It also has lessened the severity of grand mal seizures. The recovery time after has gone from around 12 hours to around 4.”
- “At first it helped a lot but my seizures have returned.”
- “Spasms – only a little better.”

Table 6.1. Patient-perceived benefit (n=792).

	No Response	1	2 or 3	4 or 5	6 or 7
All Patients	4%	4%	5%	23%	64%
Muscle Spasms	2%	3%	3%	22%	69%
Cancer	5%	5%	6%	21%	64%
Seizures	5%	5%	9%	29%	51%
Crohn's Disease	0%	2%	5%	22%	71%
Terminal Illness	11%	3%	3%	13%	71%
HIV/AIDS	4%	0%	8%	8%	79%
Tourette Syndrome	6%	0%	0%	25%	69%
Glaucoma	23%	8%	0%	0%	69%
ALS	9%	9%	0%	18%	64%

Patient responses about degree of benefit experienced: 1=no benefit; 7=great deal of benefit.

Health care practitioners were somewhat more conservative in assessment of benefit to their patients. Across all the benefit ratings by health care practitioners, 38% indicated a rating of 6 or 7 and 23% indicated little or no benefit (rating of 1, 2, or 3). Similarity in benefit assessment between health care practitioners and patients appears to vary by medical condition, with highest discrepancy among seizure patients. Descriptive comments suggest at least part of the difference is driven by perspective of what constitutes benefit. The patients cite quality of life benefits more often than the health care practitioners, who appear to focus more on objective measures such as seizure counts.

The symptom scores provided in the Patient Self-Evaluation data have the advantage of completeness, since they are required prior to each medical cannabis purchase. In this report a reduction of $\geq 30\%$ was applied to most symptoms to indicate clinically meaningful symptom reduction. In the text of the report, we present results for the more conservative of the two methods used to calculate $\geq 30\%$ symptom reduction. However, *Appendix D: Symptom Results*

from the Patient Self-Evaluation shows results for both methods (details can be found in this chapter). Results show patterns similar to those in the survey benefits rating, but usually somewhat smaller in size. For example, among patients with muscle spasms, weekly muscle spasm frequency was reduced $\geq 30\%$ within the first four months of medical cannabis use in 48% of patients (see Table 6.2). Importantly, in the four months after first achieving this degree of spasm reduction, more than half the patients retained this degree of improvement. That is, of all patients with muscle spasms, 48% achieved $\geq 30\%$ reduction in spasm frequency and 28% both achieved that degree of improvement and retained it over the next four months. Full results for symptom improvement analyses and for persistence of improvements are in *Appendix D: Symptom Results from the Patient Self-Evaluation*. Results for selected symptoms are presented in Table 6.2. For most symptoms, between half and two-thirds of patients who achieve clinically meaningful improvement retained that degree of improvement over the next four months.

Examples of proportion of patients achieving and retaining $\geq 30\%$ symptom reduction include:

- Among seizure patients, 68% reported $\geq 30\%$ reduction in seizure frequency and 49% both achieved that level of reduction and retained it, on average, for at least four months
- Among patients with Tourette syndrome, 61% reported $\geq 30\%$ reduction in tic frequency and 46% both achieved that level of reduction and retained it, on average, for at least four months
- Among patients with Crohn's disease, 51% reported $\geq 30\%$ reduction in number of liquid stools per day and 29% both achieved that level of reduction and retained it, on average, for at least four months
- Among patients with severe, persistent muscle spasms, 48% reported $\geq 30\%$ reduction in spasm frequency and 28% both achieved that level of reduction and retained it, on average, for at least four months
- Among cancer patients with at least moderate levels of nausea when they started using medical cannabis, 38% reported $\geq 30\%$ reduction of nausea and 23% both achieved that level of reduction and retained it, on average, for at least four months
- Among cancer patients with at least moderate levels of pain when they started using medical cannabis, 29% reported $\geq 30\%$ reduction of pain and 12% both achieved that level of reduction and retained it, on average, for at least four months

Moderate to severe levels of non-disease-specific symptoms such as fatigue, anxiety, and sleep difficulties were common across all the medical conditions. And the reductions in these symptoms was often quite large. These findings support the understanding that some of the benefit perceived by patients is expressed as improved quality of life.

The type(s) of medical cannabis used at the time patients achieved clinically meaningful improvement was analyzed for each symptom assessed within each category of medical condition. Full results of those analyses are in *Appendix D: Symptom Results from the Patient Self-Evaluation* and summaries are presented in this chapter. In most cases, a few combinations

of product types were purchased more frequently than others when analyzing data by patient condition

Table 6.2 Symptom improvement for selected symptoms. Note: for spasticity, pain, appetite, nausea, and vomiting the analysis was conducted on patients with moderate to severe symptoms at baseline.

	% of Patients who Achieved Threshold Symptom Improvement (≥30% Improvement Unless Otherwise Noted)	% of All Patients that Both Achieved Threshold Symptom Improvement and Retained that Degree of Improvement for at Least 4 Months
MUSCLE SPASMS		
Weekly spasm frequency (n = 629)	48%	28%
Spasticity (n = 618)	36%	17%
Pain (n = 640)	34%	17%
CANCER		
Pain (n = 356)	29%	12%
Appetite (n = 321)	39%	22%
Nausea (n = 283)	38%	23%
Vomiting (n = 168)	48%	27%
SEIZURES		
Weekly seizure frequency (n = 262)	68%	49%
CROHN'S DISEASE		
# Liquid stools/day (n = 41)	51%	29%
Abdominal pain (details in text; n = 73)	53%	19%
General well-being (details in text; n = 15)	47%	13%
Measures Combined (details in text; n = 102)	51%	22%
Weight (≥ 3 pound gain; n = 102)	21%	12%
TERMINAL ILLNESS		
Pain (n = 72)	19%	10%
Appetite (n = 64)	38%	17%
Nausea (n = 56)	45%	29%
Vomiting (n = 35)	57%	29%
HIV/AIDS		
Pain (n = 45)	40%	20%
Appetite (n = 39)	49%	31%
Weight (≥ 3 pound gain; n = 48)	15%	6%
TOURETTE SYNDROME		
Weekly tic frequency (n = 28)	61%	46%
GLAUCOMA (see text)		
ALS		
Weekly spasm frequency (n = 18)	33%	22%
Spasticity (n = 15)	20%	20%
Pain (n = 17)	47%	12%

Benefits Reported on Surveys

In addition to collecting data on severity of symptoms related to each patient's qualifying condition or conditions before each medical cannabis purchase, the Office of Medical Cannabis sought to gain a qualitative understanding of patient-reported benefits and harms of program participation. Utilizing expertise within the Minnesota Department of Health, the Office of Medical Cannabis developed a Patient Experience survey, which captures information on benefits and harms of program participation. A parallel survey was developed for each patient's certifying health care practitioner, which captures similar information from the clinician's perspective. The surveys include scaled response and open-response questions; health care practitioners were also asked to provide any clinical observations they noted about the patient's experience with medical cannabis. Healthcare providers familiar with the program provided feedback as part of the development process.

Survey Methodology and Data Preparation

The surveys are provided through an online platform with a hard copy alternative. The Patient Experience survey is sent three months after the patient's first medical cannabis purchase, six months after the first purchase and every six months thereafter. Healthcare practitioner surveys are sent six months after the patient's first purchase and every six months thereafter. Surveys are accessible through the patient or healthcare practitioner's registry page and through introductory emails containing unique links. To maximize survey submission rates, the survey can be submitted with incomplete responses to any of the questions. Each of the surveys is available online to the recipient for 45 days. Patient recipients receive reminder emails after one week; after two weeks with no response, paper copies of surveys are mailed to the recipient. For patients without online access the full process is accomplished by mail.

Initially, patient and healthcare practitioners (HCPs) were sent one survey three months after the patient's first purchase, without recurrence. This schedule was revised to include recurring surveys roughly every six months to provide patients and their HCPs an opportunity to report ongoing progress or changes to the patient's condition; however the HCP survey sent three months after the first purchase was eliminated based on feedback that three months may not allow enough time for the provider to see their patient following initial certification. These changes were implemented in April 2016; as a result, HCP survey data collected three months after the first purchase is only available for the first six months of the program (this includes patients who enrolled and made a first purchase between July 1, 2015 and December 31, 2015). All survey data presented in this chapter are from the patient and health care practitioner surveys sent three months after the patient's first medical cannabis purchase.

Patients and their certifying HCPs were asked to report the "most important benefit" and "most important negative effect" related to medical cannabis treatment. Survey responses from patients and health care practitioners on perceived benefits and perceived negative effects

were reported in free-text format; each response was individually reviewed and classified into a category of benefit or negative effects. Reported benefits typically included either direct improvement of symptoms related to the patient’s qualifying condition or more general improvements in health or quality of life, referred to in this report as global health benefits. Additionally, many responses included more than one type of benefit; in these cases, the first reported benefit was presumed to be the most important benefit. In this report, we examine both overall perceptions of benefit, as well as type of reported benefit.

Patient Experience Survey Results

Patient Experience Survey Response Rate

Of 1491 patients who were approved and made their first medical cannabis purchase in the first year of the program (July 1, 2015- June 30, 2016), 792 patients (53%) submitted a survey three months after making the first purchase. As of December 31, 2016, 90 patients (5%) were known to be deceased since enrolling in the program. These patients were included in this report, as in some cases caregivers or relatives and HCPs completed surveys, reflecting on the patient’s experience for the period of time the patient did use medical cannabis.

Table 6.3. Patient survey response rates by age group.

	Total	Patient Responses
0-4	62	17 (53%)
5-17	129	76 (59%)
18-24	89	51 (57%)
25-35	234	132 (56%)
36-49	355	192 (54%)
50-64	462	258 (56%)
65+	160	66 (41%)
Total	1491	792 (53%)

Table 6.4. Patient total counts and patient response rates by qualifying medical condition.

	Total	Patient Responses
Muscle Spasms	653	373 (57%)
Cancer	386	157 (41%)
Seizures	287	182 (63%)
Crohn's Disease	99	55 (56%)
Terminal Illness	79	38 (48%)
HIV/AIDS	46	24 (52%)
Tourette Syndrome	28	16 (57%)
Glaucoma	21	13 (62%)
ALS	21	11 (52%)

Table 6.5. Patient survey response rates by race and ethnicity.

	Total	Patient Responses
American Indian	37	14 (38%)
Asian	24	8 (33%)
Black	86	35 (41%)
Hawaiian	3	0 (0%)
White	1249	712 (57%)
Other	24	9 (38%)
Hispanic	35	14 (40%)

Patient response rates varied across age group, qualifying condition and race and ethnicity (Tables 6.3-6.5). Elderly patients (ages 65 and over) had the lowest response rate (41%); patients certified for cancer and terminal illness also had low response rates relative to other certified condition groups (41% and 48%, respectively). In general, racial and ethnic minorities were under-represented in survey responses.

Patient Perceptions of Benefits from Medical Cannabis

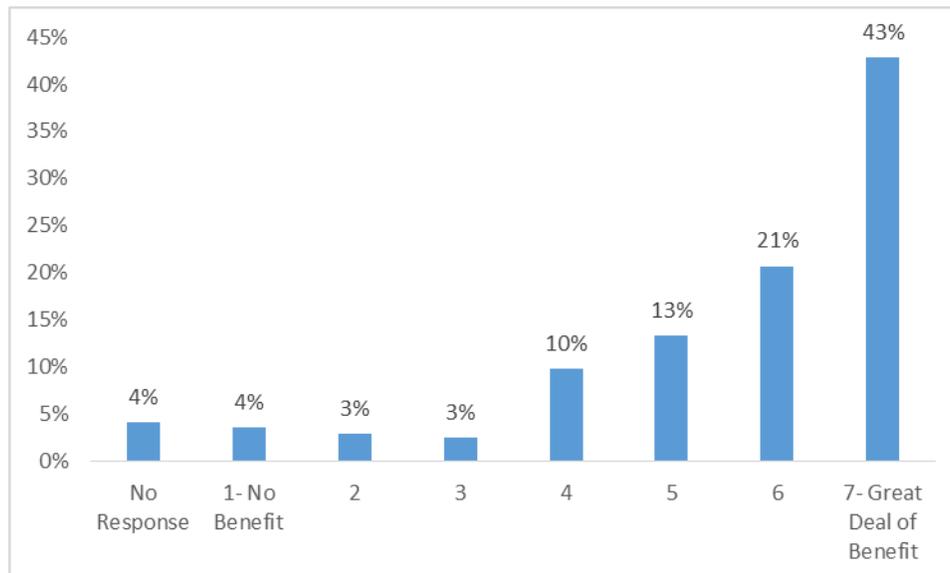
The Patient Experience and HCP surveys both ask respondents to report how much benefit they believe the patient received from using medical cannabis, on a scale from 1 (no benefit) to 7 (a great deal of benefit). Figures 6.1-6.10 show the distribution of benefit scores on this scale, as reported by patients, for all patients and by patients with each qualifying condition.

The percentages in Figures 6.1-6.10 are based on the total number of patient responses in each condition group and not the number of complete benefit scores for each group (33 patients submitted surveys without completing the benefit score question, but were included in the denominators).

ALL QUALIFYING CONDITIONS

Figure 6.1 below shows all patient responses about degree of benefit experienced. Among patient respondents, 43% report the highest degree of benefit from medical cannabis: “a great deal of benefit” or a score of 7 on a scale from 1-7.

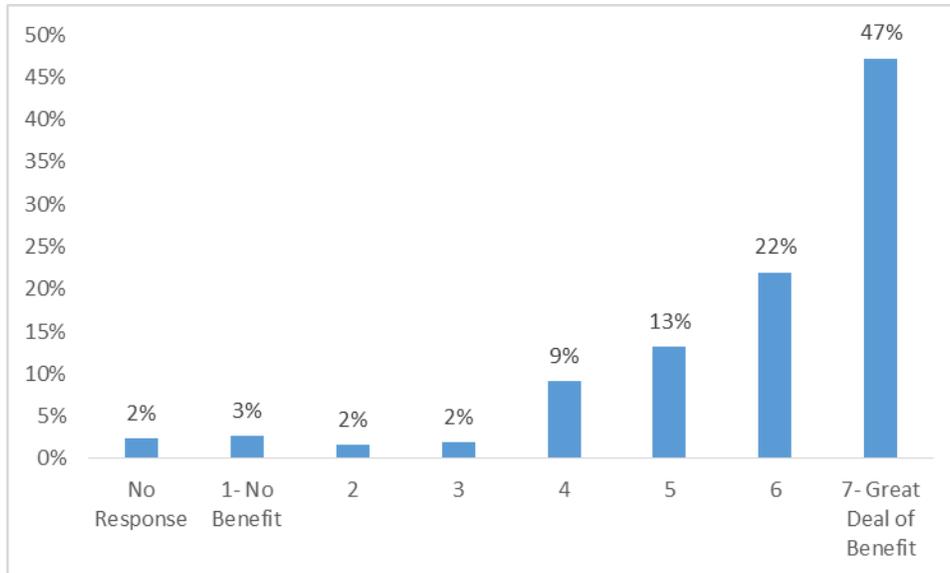
Figure 6.1. Patient-Perceived Benefit: All Conditions (N=792).



SEVERE AND PERSISTENT MUSCLE SPASMS

Figure 6.2 shows responses from patients certified for severe and persistent muscle spasms regarding degree of benefit experienced. Among respondents, 47% report a score of 7 on a scale from 1-7.

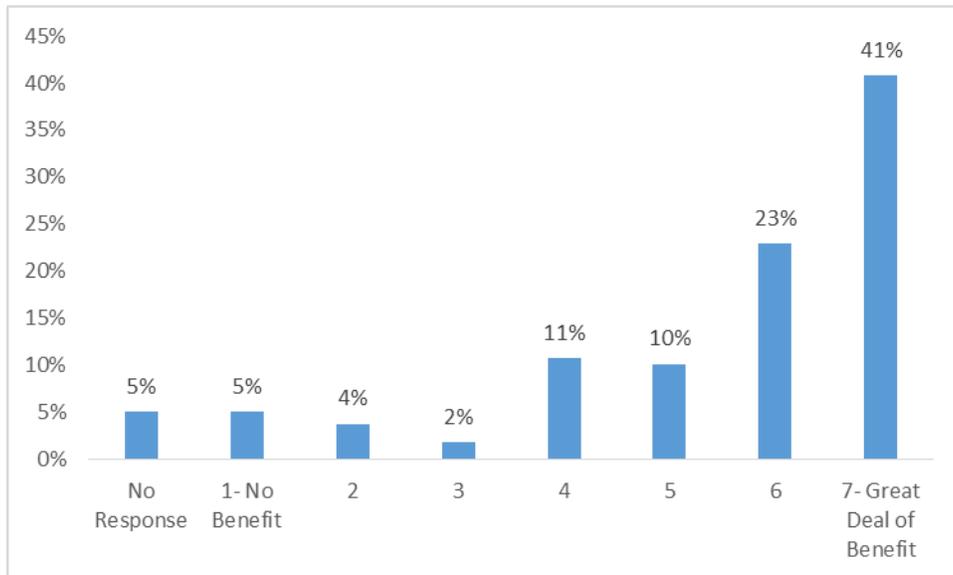
Figure 6.2. Patient-Perceived Benefit: Muscle Spasms (N=373)



CANCER

Figure 6.3 shows responses from patients certified for cancer regarding degree of benefit experienced. Among respondents, 41% report a score of 7 on a scale from 1-7.

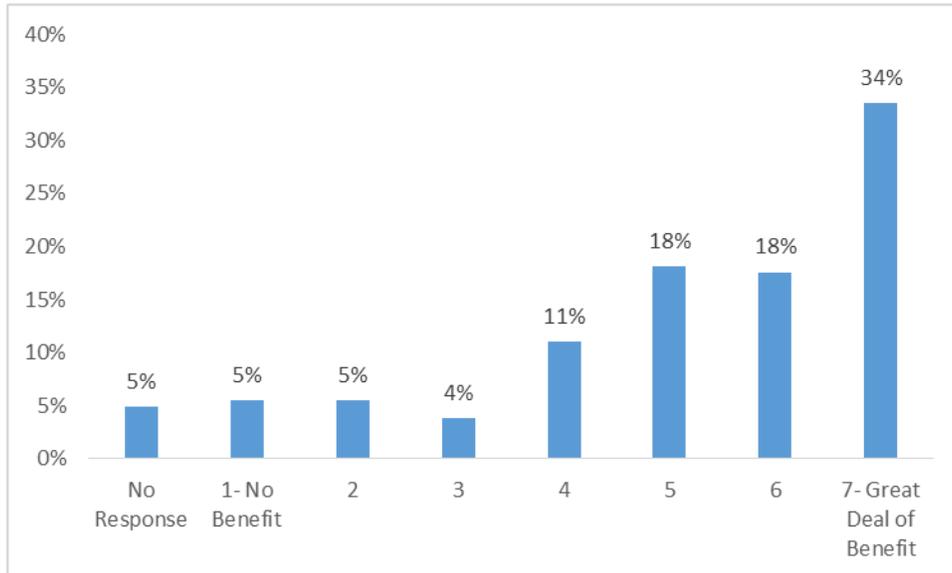
Figure 6.3. Patient-Perceived Benefit: Cancer (N=157)



SEIZURES

Figure 6.4 shows responses from patients certified for seizure disorders regarding degree of benefit experienced. Among respondents, 34% report a score of 7 on a scale from 1-7.

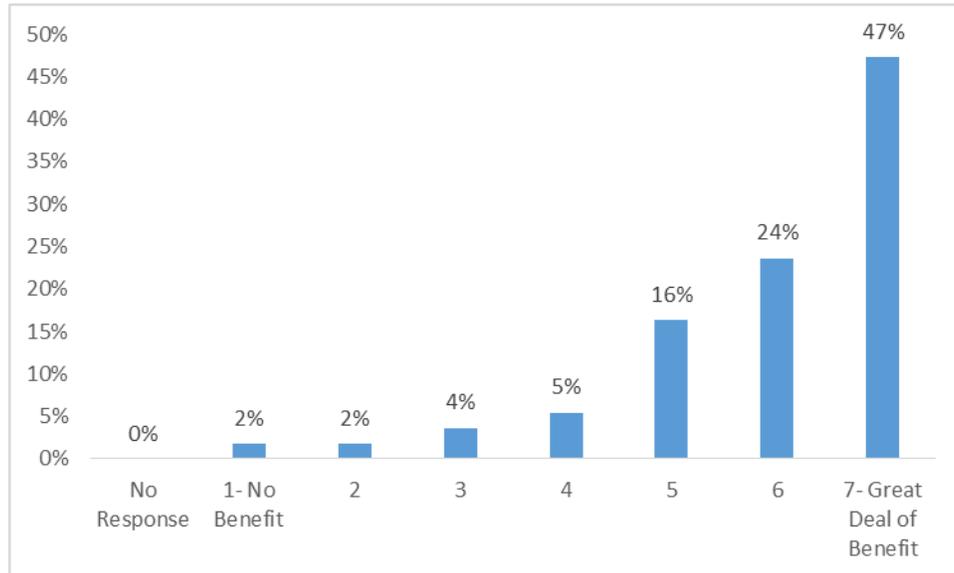
Figure 6.4. Patient-Perceived Benefit: Seizures (N=182)



CROHN'S DISEASE

Figure 6.5 shows responses from patients certified for Crohn's disease regarding degree of benefit experienced. Among respondents, 47% report a score of 7 on a scale from 1-7.

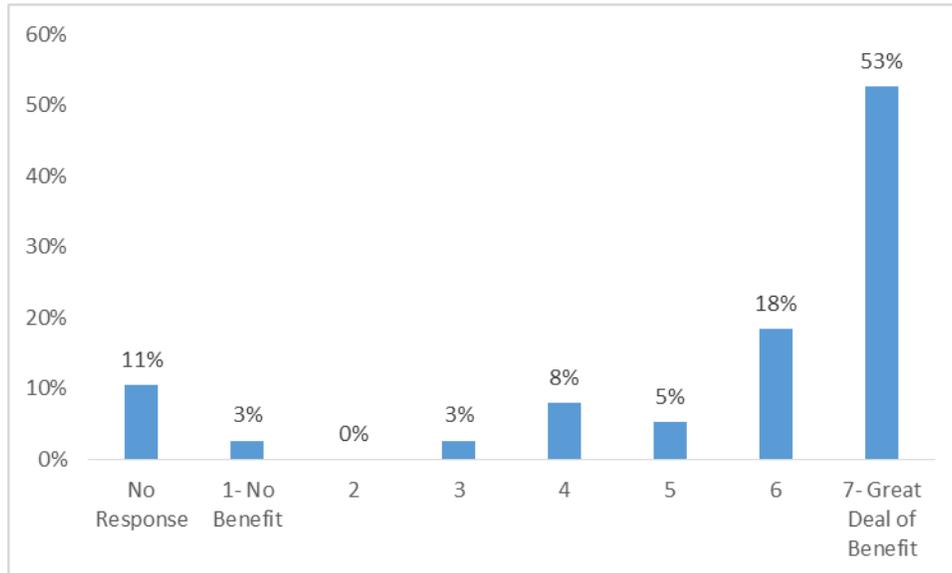
Figure 6.5. Patient-Perceived Benefit: Crohn's Disease (N=55)



TERMINAL ILLNESS

Figure 6.6 shows responses from patients certified for terminal illness regarding degree of benefit experienced. Among respondents, 53% report a score of 7 on a scale from 1-7.

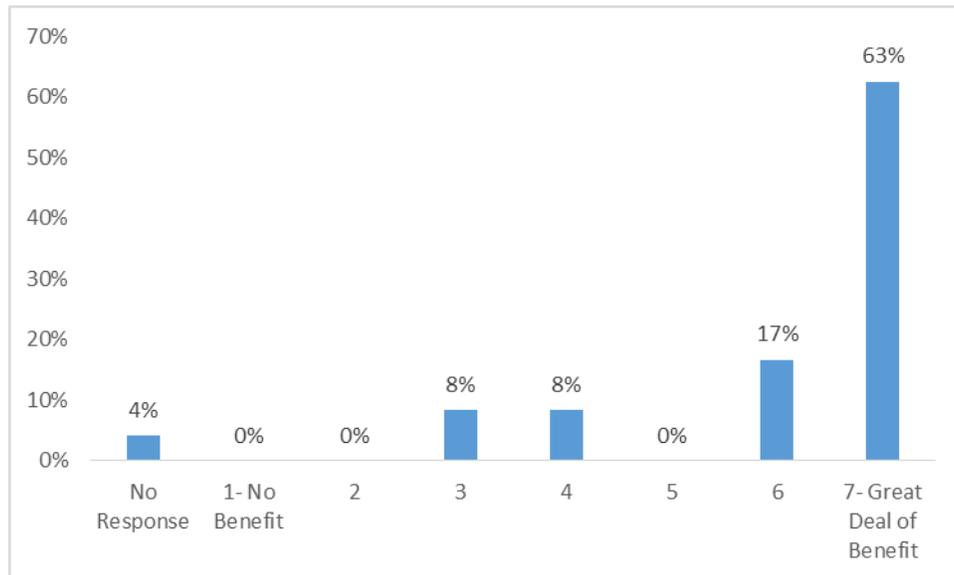
Figure 6.6. Patient-Perceived Benefit: Terminal Illness (N=38)



HIV/AIDS

Figure 6.7 shows responses from patients certified for HIV/AIDS regarding degree of benefit experienced. Among respondents, 63% report a score of 7 on a scale from 1-7.

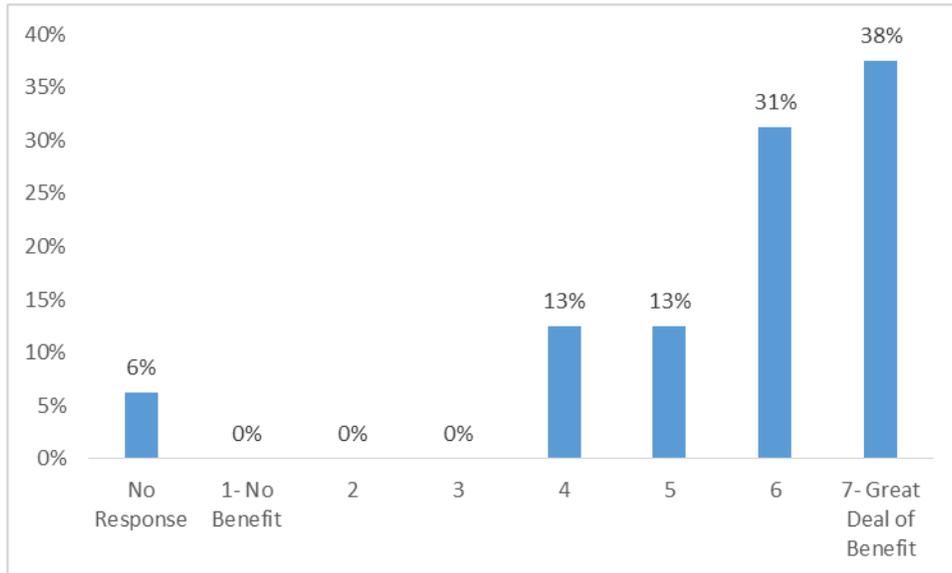
Figure 6.7. Patient-Perceived Benefit: HIV/AIDS (N=24)



TOURETTE SYNDROME

Figure 6.8 shows responses from patients certified for Tourette syndrome regarding degree of benefit experienced. Among respondents, 38% report a score of 7 on a scale from 1-7.

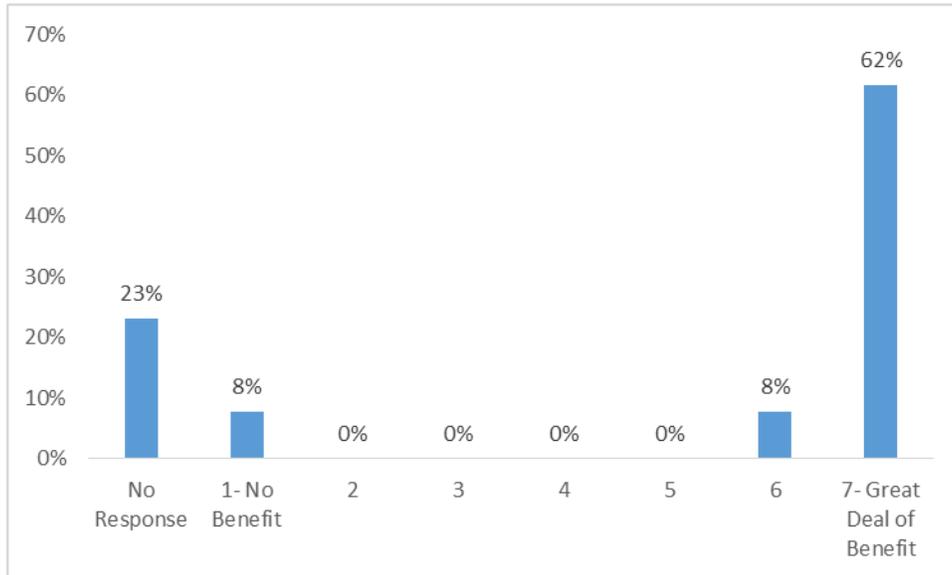
Figure 6.8. Patient-Perceived Benefit: Tourette Syndrome (N=16)



GLAUCOMA

Figure 6.9 shows responses from patients certified for glaucoma regarding degree of benefit experienced. Among respondents, 62% report a score of 7 on a scale from 1-7.

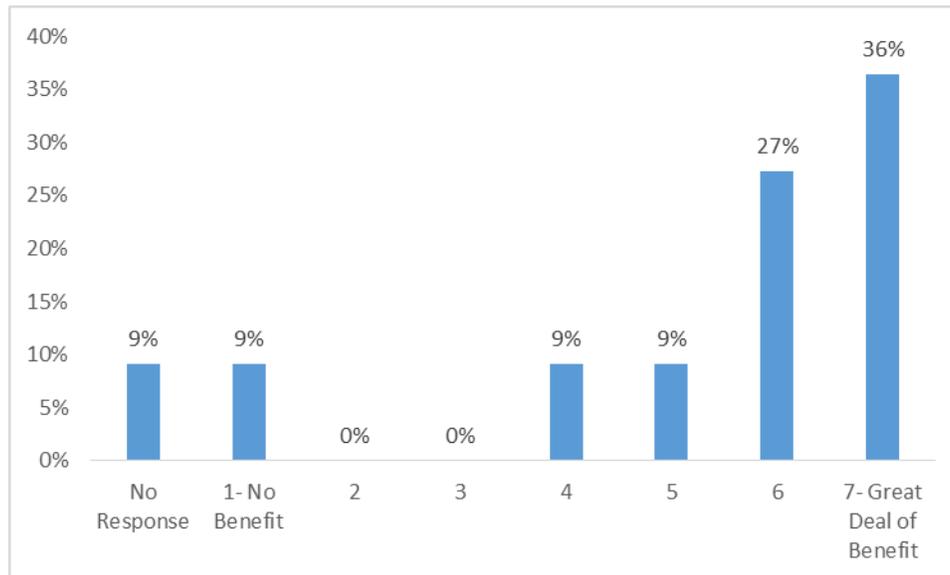
Figure 6.9. Patient-Perceived Benefit: Glaucoma (N=13)



ALS

Figure 6.10 shows responses from patients certified for ALS regarding degree of benefit experienced. Among respondents, 36% report a score of 7 on a scale from 1-7.

Figure 6.10. Patient-Perceived Benefit: ALS (N=11)



Patient Perceptions of Types of Benefits from Medical Cannabis Treatment

In both the Patient Experience and HCP surveys, patients and their certifying HCPs had an opportunity to describe the most significant benefit to the patient that was associated with medical cannabis treatment. Each response was reviewed and classified as symptom improvement (based on qualifying condition), or global health benefit, which included all health benefits not specifically related to the relief of symptoms directly associated with the patient's qualifying medical condition(s). Note that not all completed surveys had a response for this question; 86% of the Patient Experience surveys did and 66% of the HCP surveys did. Among the 681 completed Patient Experience survey responses that indicated a most significant benefit, 64% classified the benefit as symptom improvement and 25% classified it as a global health benefit; the remaining comments regarding benefit were improvement of symptoms other than those related to the qualifying condition or global health benefits. Tabulation of those responses is reported below, but the reader is also encouraged to read the verbatim responses in *Appendix A: Patient-Reported Benefits from Surveys*. Reading the words written by the patient gives a more nuanced understanding of the benefits and provides a reminder that each of the respondents is an individual person. The following is a selection of the comments, chosen to reflect the full range of benefits perceived:

- “Almost all muscle spasms and pain associated with spasms are gone. I used to have constant nerve triggered pain that is minimal now. Results were almost immediate. I am sleeping way better now also.”
- “A large reduction in symptoms, allowing me to participate in my daily life without a large number of limits my symptoms would place on me – stools decreased from over 8 a day to about 2 with much less blood and mucous in stools. Pain has reduced to a tolerable amount”
- “[NAME] has passed away. I am her daughter and was her care giver. She was open to trying medical cannabis and we got the liquid form. It was a saving grace. She was in a lot of pain and when prescribed medications did NOT work – we started this and it kept her calm and relaxed. I am very thankful that we were able to have this option available. It helped to make her last months more bearable and truly it would have been miserable without it.”
- “Has eased my muscle spasms and cramping. Has helped my visual issues. Has helped me to maintain healthy weight. Have been able to sleep much better and have cut other pain prescriptions way back. Seems to take pain away enough that I have been more active and am able to function on household tasks to a somewhat normal level. My brain seems to be working better as well ie. concentration/focusing and remembering.”
- “I am getting enough sleep for the first time since about 2011. My absence seizures have gone from 3-4 a day to almost 0. It also has lessened the severity of grand mal seizures. The recovery time after has gone from around 12 hours to around 4.”
- “Within 1 week of use, my tics disappeared and have stayed gone even with occasional use. This has never happened previously in my life, so it is very effective.”
- “At first it helped a lot but my seizures have returned.”
- “Spasms – only a little better.”

Symptom Improvement from Medical Cannabis Treatment

Table 6.6 summarizes the reported “most important benefits” which could be considered improvement of a symptom related to the patient’s qualifying condition from reports of patients, categorized by the benefit score reported by the patient. For patients with severe muscle spasms, reports of spasm reduction or pain reduction were considered symptom improvement. For patients with cancer (regardless of whether their condition was associated with severe/chronic pain, nausea or severe vomiting, cachexia or severe wasting, or a combination), pain reduction, nausea and/or vomiting reduction, and weight gain and/or appetite improvement were considered symptom improvement. For patients with seizures, reports of fewer seizures, less severe seizures, or both, were considered symptom improvement. For patients with Crohn’s disease, pain reduction, weight gain and/or appetite improvement, and reduction in related symptoms including stool frequency were considered symptom improvement. For patients with terminal illnesses (regardless of whether their condition was associated with severe/chronic pain, nausea or severe vomiting, cachexia or

severe wasting, or a combination), reduction in pain, nausea and/or vomiting and weight gain and/or appetite improvement were considered symptom improvement. For patients certified for HIV/AIDS, reduction in pain, nausea and/or vomiting, and weight gain and/or appetite improvement were considered symptom improvement. In patients with Tourette syndrome, reduced tics or specific mention of reduced Tourette symptoms were considered symptom improvement. In patients certified for glaucoma, reduction in intraocular pressure or reference to treatment of glaucoma “symptoms” was considered symptom improvement. Finally, for patients with ALS, reduction in pain or spasms were considered symptom improvement.

Among patients with severe and persistent muscle spasms, 26% reported pain reduction and another 25% reported spasm reduction as the most important benefit. Among seizure patients, 51% reported seizure reduction (either in frequency or severity). Among cancer patients, 26% reported pain reduction as the primary benefit; 25% reported weight gain, appetite improvement, or reduced nausea or vomiting. Among Crohn’s disease respondents, 25% reported reduced pain, 16% reported reduced severity or frequency of gastrointestinal symptoms and 4% reported weight gain or appetite improvement as the primary benefit. Among patients with terminal illness, 21% reported reduced nausea or vomiting, 18% reported pain reduction and 8% reported weight gain or appetite improvement as the most important benefit. Thirty-one percent of glaucoma patient respondents reported reduction of glaucoma-related symptoms. Among ALS patients, 27% reported pain reduction and 9% reported spasm reduction as the most important benefit. Among HIV/AIDS patients, 25% reported reduced pain, 17% reported reduced nausea and/or vomiting and 12% reported weight gain or appetite improvement as the most important benefit. Finally, among patients with Tourette syndrome, 63% reported a reduction in tics or other symptoms of Tourette syndrome.

Table 6.6. Distribution of Symptom Improvement by Condition: Patient Surveys

	1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
Muscle Spasms (n=373)								
<i>Spasm Reduction</i>	-	-	1 (0%)	11 (3%)	14 (4%)	24 (6%)	45 (12%)	95 (25%)
<i>Pain Reduction</i>	-	-	2 (1%)	6 (2%)	17 (5%)	24 (6%)	48 (13%)	97 (26%)
Cancer (n=157)								
<i>Pain Reduction</i>	-	-	-	3 (2%)	9 (6%)	12 (8%)	17 (11%)	41 (26%)

	1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
<i>Reduced Nausea/Vomiting</i>	-	-	-	1 (1%)	2 (1%)	2 (1%)	14 (9%)	19 (12%)
<i>Weight Gain/Appetite Improvement</i>	-	1 (1%)	-	2 (1%)	1 (1%)	6	10 (6%)	20 (13%)
Seizures (n=182)								
<i>Seizure Reduction</i>	-	3 (2%)	4 (2%)	9 (5%)	15 (8%)	22 (11%)	39 (21%)	92 (51%)
Crohn's Disease (n=55)								
<i>Pain Reduction</i>	-	-	-	-	3 (5%)	4 (5%)	7 (13%)	14 (25%)
<i>Reduced Crohn's Symptoms</i>	-	-	-	-	-	2 (4%)	7 (13%)	9 (16%)
<i>Weight Gain/Appetite Improvement</i>	-	-	-	-	1 (2%)	1 (2%)	-	2 (4%)
Terminal Illness (n=38)								
<i>Reduced Nausea/Vomiting</i>	-	-	-	1 (3%)	-	1 (3%)	6 (16%)	8 (21%)
<i>Pain Reduction</i>	-	-	-	1 (3%)	1 (3%)	-	5 (13%)	7 (18%)
<i>Weight Gain/Appetite Improvement</i>	-	-	-	-	-	-	3 (8%)	3 (8%)
HIV/AIDS (n=24)								
<i>Pain Reduction</i>	-	-	1 (4%)	1 (4%)	-	3 (13%)	3 (13%)	6 (25%)
<i>Reduced Nausea/Vomiting</i>	-	-	-	-	-	-	4 (17%)	4 (17%)

	1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
<i>Weight Gain/Appetite Improvement</i>	-	-	1 (4%)	-	-	-	2 (8%)	3 (12%)
Tourette Syndrome (n=16)								
<i>Reduced Tics/Tourette Symptoms</i>	-	-	-	-	1 (6%)	4 (25%)	5 (31%)	10 (63%)
Glaucoma (n=13)								
<i>Reduced Glaucoma Symptoms</i>	-	-	-	-	-	1 (8%)	3 (23%)	4 (31%)
ALS (n=11)								
<i>Spasm Reduction</i>	-	-	-	-	-	1 (9%)	-	1 (9%)
<i>Pain Reduction</i>	-	-	-	-	-	1 (9%)	2 (18%)	3 (27%)

Patient Perceptions of Global Health Benefits from Medical Cannabis

Many patients responded to the question regarding “most important benefit” by describing benefits not specifically related to the symptoms of their qualifying conditions. These responses were reviewed and classified into categories of “global health benefits”- broader benefits which impact the patient’s overall health. Global health benefits reported by patients included improvement in quality of life, improvement in sleep (whether or not explicitly tied to reduction in symptoms related to qualifying condition), improved mobility and/or ability to function or perform regular tasks, reduced anxiety or increased calmness, improved alertness and/or cognitive functioning, and reduced usage of other medications (often reported as reduction in dosage and/or side effects related to use of other medications). Clearly, global health benefits may be due to improvements in symptoms specifically related to the qualifying condition, so the dividing line between these categories is a bit blurry.

Table 6.7 shows the number of responses by type of global health benefit, along with the associated benefit score reported by the patient. Overall, 6% of patient respondents reported

improved sleep as the most important benefit from medical cannabis; 4% reported improved quality of life, 4% reported reduced usage of other medication, 3% reported reduced anxiety, and 2% reported improved alertness or cognitive function.

Table 6.7. Distribution of Global Health Benefits Condition: Patient Surveys

	1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
Muscle Spasms (n=373)								
<i>Weight Gain/ Appetite Improvement</i>	-	-	-	-	1 (0%)	3 (1%)	2 (1%)	6 (2%)
<i>Improved Alertness/ Cognitive Functioning</i>	-	-	-	-	-	-	1 (0%)	1 (0%)
<i>Improved Quality of Life</i>	-	-	2 (1%)	1 (0%)	1 (0%)	3 (1%)	10 (3%)	17 (5%)
<i>Improved Sleep</i>	-	1 (0%)	-	5 (1%)	7	4 (1%)	8 (2%)	25 (7%)
<i>Improved Mobility/Ability to Function</i>	-	1 (0%)	-	-	-	1 (0%)	10 (3%)	12 (3%)
<i>Decreased Anxiety</i>	-	1 (0%)	-	1 (0%)	-	5 (1%)	4 (1%)	11 (3%)
<i>Reduced Dosage and/or Side Effects of Other Medications</i>	-	-	-	-	-	2 (1%)	16 (4%)	18 (5%)
Cancer (n=157)								
<i>Reduced Anxiety</i>	-	1 (1%)	-	2 (1%)	-	1 (1%)	2 (1%)	6 (4%)
<i>Improved Sleep</i>	-	-	1 (1%)	2 (1%)	2 (1%)	1 (1%)	5 (3%)	11 (7%)
<i>Improved Quality of Life</i>	-	-	-	1 (1%)	-	2 (1%)	1 (1%)	4 (3%)
<i>Improved Alertness/Cognitive Functioning</i>	-	-	-	-	-	-	1 (1%)	1 (1%)

	1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
<i>Reduced Dosage and/or Side Effects of Other Medications</i>	-	-	-	-	-	2 (1%)	3 (2%)	5 (3%)
Seizures (n=182)								
<i>Decreased Anxiety</i>	-	1 (1%)	-	-	1 (1%)	-	-	2 (1%)
<i>Improved Sleep</i>	-	-	-	-	-	1 (1%)	1 (1%)	2 (1%)
<i>Reduced Dosage and/or Side effects of Other Medications</i>	-	-	-	-	1 (1%)	1 (1%)	3 (2%)	5 (3%)
<i>Improved Quality of Life</i>	-	-	-	-	2 (1%)	1 (1%)	4 (2%)	7 (4%)
<i>Improved Alertness/Cognitive Functioning</i>	-	2 (1%)	1 (1%)	3 (2%)	2 (1%)	5 (3%)	4 (2%)	17 (9%)
Crohn's Disease (n=55)								
<i>Improved Quality of Life</i>	-	-	-	1 (2%)	-	-	5 (9%)	6 (11%)
<i>Improved Sleep</i>	-	-	1 (2%)	2 (4%)	2 (4%)	1 (2%)	-	6 (11%)
<i>Decreased Anxiety</i>	-	-	-	-	1 (2%)	2 (4%)	-	3 (5%)
Terminal Illness (n=38)								
<i>Decreased Anxiety</i>	-	-	-	-	-	1 (3%)	-	1 (3%)
<i>Improved Alertness/ Cognitive Functioning</i>	-	-	-	-	-	-	1 (3%)	1 (3%)
<i>Improved Sleep</i>	-	-	1 (3%)	1 (3%)	-	-	2 (5%)	4 (11%)

	1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
<i>Improved Quality of Life</i>	-	-	-	-	-	2 (5%)	1 (3%)	3 (8%)
HIV/AIDS (n=24)								
<i>Improved Sleep</i>	-	-	-	-	-	-	1 (4%)	1 (4%)
<i>Decreased Anxiety</i>	-	-	-	-	-	-	2 (8%)	2 (8%)
Tourette Syndrome (n=16)								
<i>Improved Quality of Life</i>	-	-	-	-	-	-	1 (6%)	1 (6%)
<i>Decreased Anxiety</i>	-	-	-	1 (6%)	-	1 (6%)	-	2 (13%)
Glaucoma (n=13)								
<i>Improved Quality of Life</i>	-	-	-	-	-	-	1 (8%)	1 (8%)
ALS (n=11)								
<i>Reduced Anxiety</i>	-	-	-	1 (9%)	-	1 (9%)	1 (9%)	3 (27%)
<i>Improved Sleep</i>	-	-	-	-	1 (9%)	-	1 (9%)	2 (18%)

Health Care Practitioner Survey Results

HCP Survey Response Rate

As a result of changing the survey schedule during the first program year, the healthcare providers of 774 patients who were enrolled and made a first medical cannabis purchase in the first six months of the program (July 1 – December 31, 2015) received a survey three months after the patient’s first purchase; the remaining 717 could therefore not be included in the reporting below. The subset of Patient Experience survey responses that corresponds to this group of HCP responses is included below for comparison. Of 774 patients in this group, 437 patients (57%) submitted a survey three months after making the first purchase. Of the 262 health care practitioners (HCP) who certified these patients, 114 (43.5%) completed surveys for 251 (32%) patients.

Table 6.8. Healthcare Practitioner and Patient Experience survey response rates by age group.

	Total	HCP Responses	Patient Responses
0-4	15	7 (47%)	9 (60%)
5-17	90	36 (40%)	49 (54%)
18-24	48	18 (38%)	28 (58%)
25-35	110	32 (29%)	59 (54%)
36-49	194	66 (34%)	114 (59%)
50-64	225	65 (29%)	131 (58%)
65+	92	27 (29%)	47 (51%)
Total	774	251 (32%)	437 (58%)

Table 6.9. Patient total counts and HCP/patient response rates by qualifying medical condition.

	Total	HCP Responses	Patient Responses
Muscle Spasms	305	98 (32%)	182 (60%)
Cancer	192	51 (27%)	84 (44%)
Seizures	189	64 (34%)	120 (63%)
Crohn's Disease	58	25 (43%)	34 (59%)
Terminal Illness	43	12 (28%)	21 (49%)
HIV/AIDS	26	12 (46%)	15 (58%)
Tourette Syndrome	11	4 (36%)	6 (55%)
Glaucoma	11	3 (27%)	5 (45%)
ALS	15	5 (33%)	7 (47%)

Table 6.10. Patient total counts and HCP/patient response rates by race and ethnicity.

	Total	HCP Responses	Patient Responses
American Indian	16	6 (38%)	7 (44%)
Asian	17	8 (47%)	7 (41%)
Black	41	14 (35%)	15 (37%)
Hawaiian	1	0 (0%)	0 (0%)
White	665	218 (33%)	395 (59%)
Other	14	5 (36%)	6 (43%)
Hispanic	18	4 (22%)	6 (33%)

Response rates for the Patient Experience and HCP surveys varied widely across age group, qualifying condition and race and ethnicity (Tables 6.8-6.10). Patient response rate was lowest among the oldest age group (65+; 51%) and HCP response rate was generally lower for older age groups. Among HCP responses, certifiers of patients with HIV/AIDS and Crohn’s disease had the highest response rates (46% and 43%, respectively). Among patient responses, patients certified for severe and persistent muscle spasms, seizures and Crohn’s disease had the highest response rates (60%, 63%, and 59%, respectively). Finally, racial and ethnic minorities were generally under-represented among patient responses.

Healthcare Practitioner Perceptions of Benefit

The Patient Experience and HCP surveys both ask respondents to report how much benefit they believe the patient received from using medical cannabis, on a scale from 1 (no benefit) to 7 (a great deal of benefit). Figures 6.11-6.20 show the distribution of benefit scores on this scale, as reported by HCPs, for all patients and by patients with each qualifying condition.

A note on how proportions were calculated: the total number of HCP responses is reflected in Figures 6.11-6.20; this includes 45 HCP responses with either no response or a “0” option selected for the benefit scale, which indicates that the HCP did not have enough information about the patient to answer the question of benefit.)

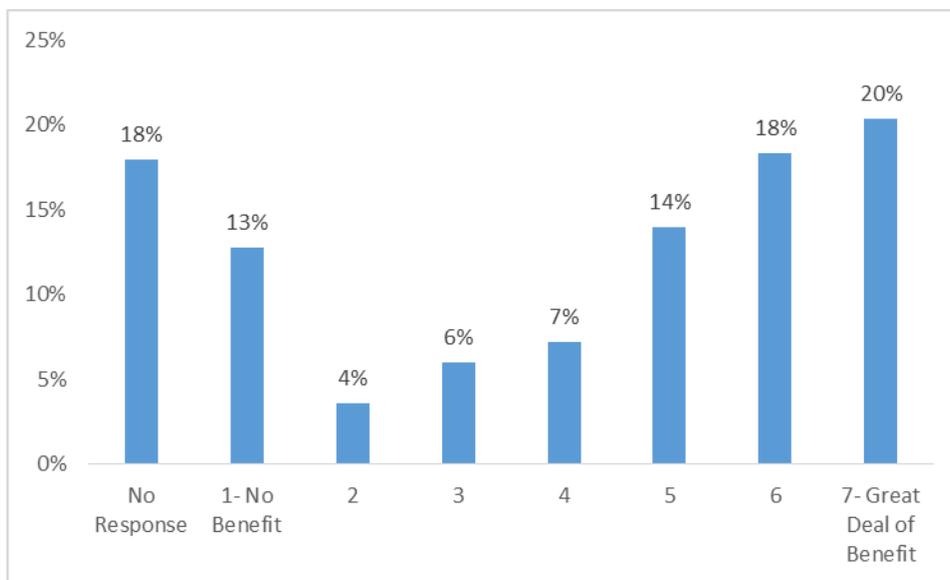
Note that results from patient surveys (Figures 6.1-6.10) and health care practitioner surveys (Figures 6.11-6.20) do not pertain to identical groups of patients. That is, some patients have

only a patient survey completed, some have only a HCP survey completed, some have neither completed, and some (n=126) have a completed survey from both the patient and their certifying HCP. For this reason, comparison of results from patient and HCP surveys must be approached with caution, except for the last group, where there is a completed survey from both the patient and the HCP. Further on in this section (Table 6.13 and Figures 6.21-6.28) comparisons for that last group are presented. In general, responses from HCPs report a lower degree of benefit than the patient responses.

ALL QUALIFYING CONDITIONS

Figure 6.11 shows all HCP responses about degree of benefit experienced. Benefit ratings were provided on 206 of the 251 submitted surveys. Among the 251 surveys, 32 (13%) reported no benefit and 51 (20%) reported the highest degree of benefit (score of 7); 150 (60%) reported a benefit score ≥ 4 on the seven-point scale.

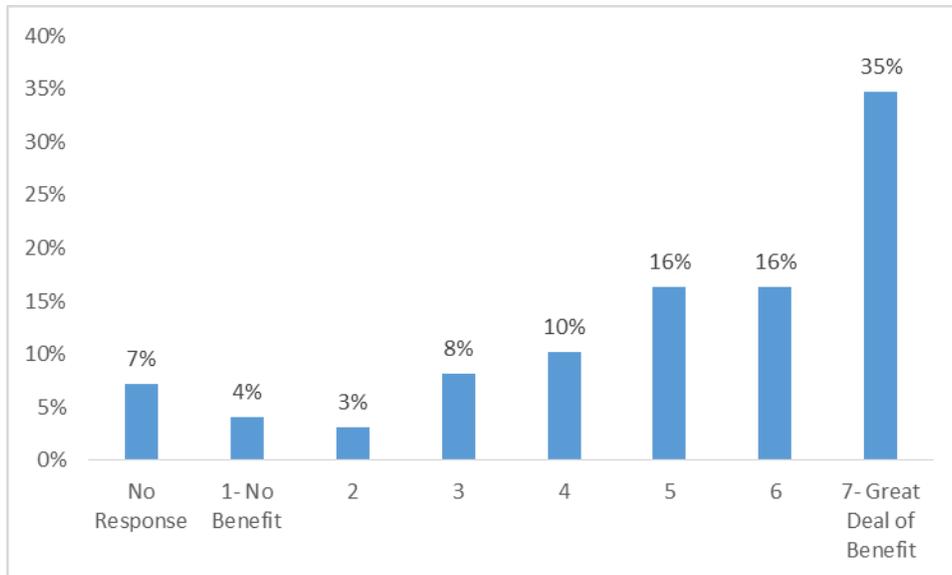
Figure 6.11. HCP-Perceived Benefit: All Conditions (N=251)



SEVERE AND PERSISTENT MUSCLE SPASMS

Figure 6.12 shows HCP benefit score responses for patients certified for severe and persistent muscle spasms. Benefit ratings were provided on 91 of the submitted surveys. Among the 91 responses, 4 reported no benefit and 34 reported the highest degree of benefit (score of 7); 76 (84%) reported a benefit score ≥ 4 on the seven-point scale.

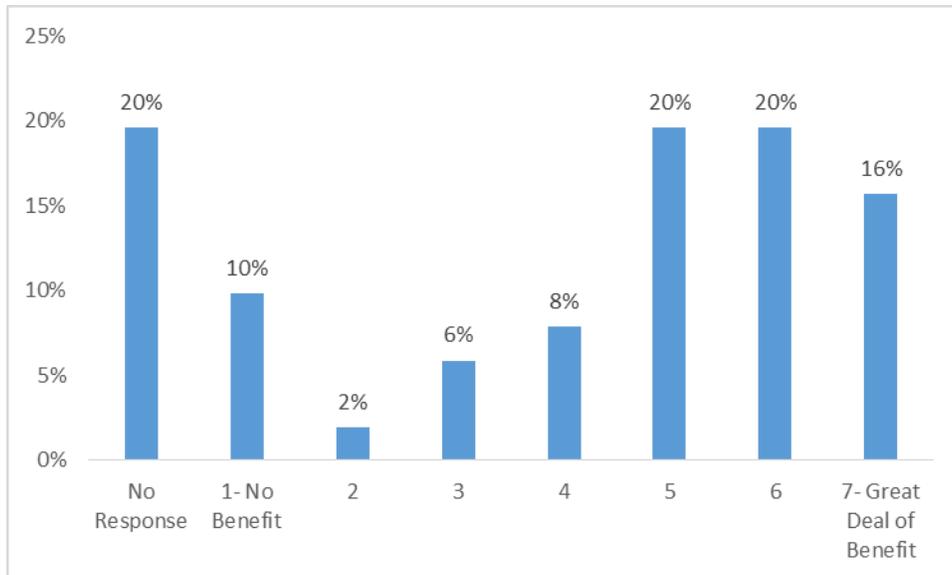
Figure 6.12. HCP-Perceived Benefit: Severe and Persistent Muscle Spasms (N=98)



CANCER

Figure 6.13 shows HCP benefit score responses for patients certified for cancer. Benefit ratings were provided on 41 of the submitted surveys. Among the 41 responses, 5 reported no benefit and 8 reported the highest degree of benefit (score of 7); 32 (78%) reported a benefit score ≥ 4 on the seven-point scale.

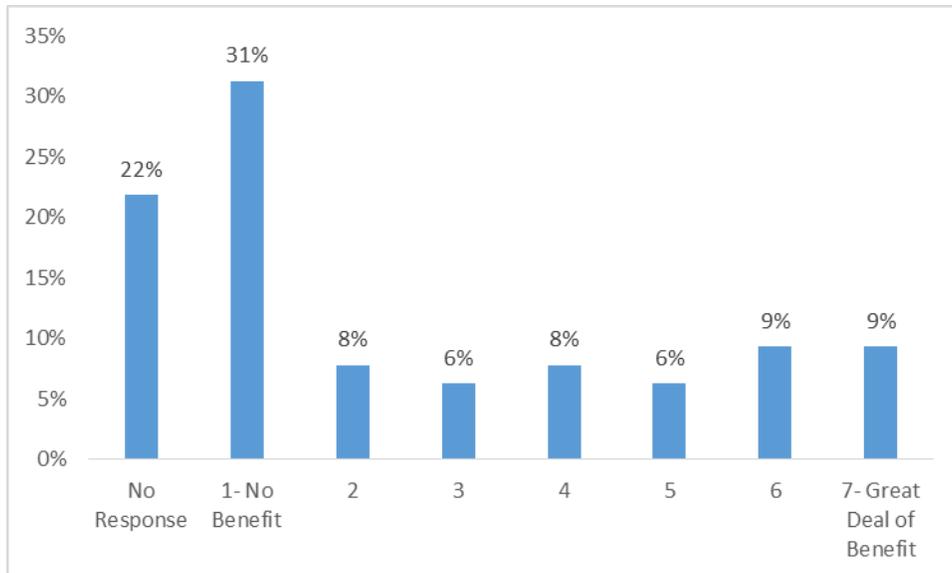
Figure 6.13. HCP-Perceived Benefit: Cancer (N=51)



SEIZURES

Figure 6.14 shows HCP benefit score responses for patients certified for seizures. Benefit ratings were provided on 50 of submitted surveys. Among the 50 responses, 20 reported no benefit and 6 reported the highest degree of benefit (score of 7); 21 (42%) reported a benefit score ≥ 4 on the seven-point scale.

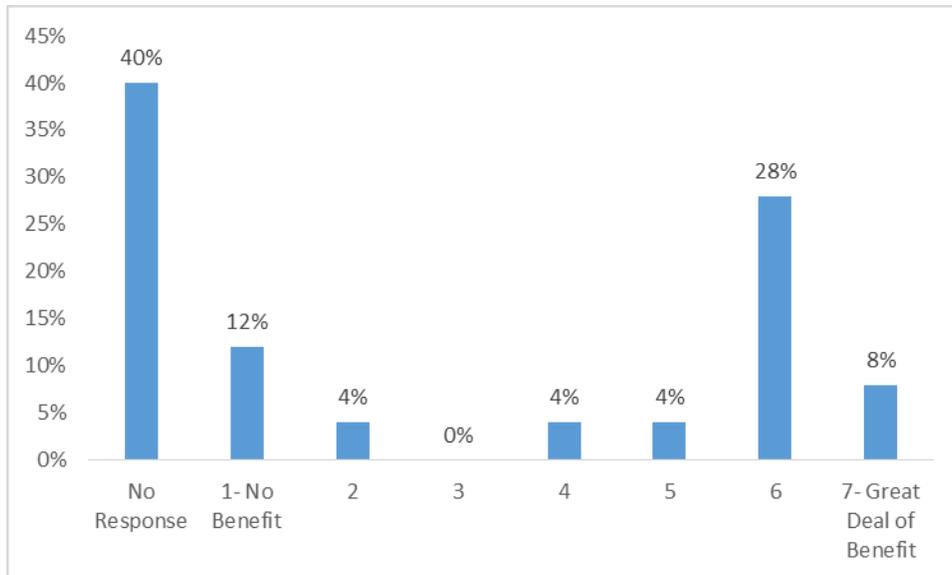
Figure 6.14. HCP-Perceived Benefit: Seizures (N=64)



CROHN'S DISEASE

Figure 6.15 shows HCP benefit score responses for patients certified for Crohn's disease. Benefit ratings were provided on 15 of the completed surveys. Among the 15 responses, 3 reported no benefit and 2 reported the highest degree of benefit (score of 7); 11 (73%) reported a benefit score ≥ 4 on the seven-point scale.

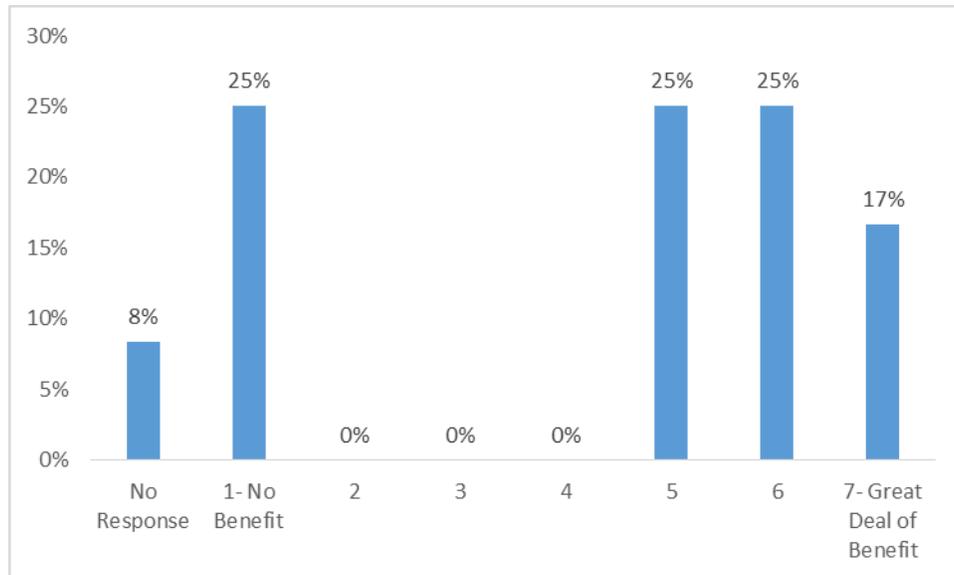
Figure 6.15. HCP-Perceived Benefit: Crohn's Disease (N=25)



TERMINAL ILLNESS

Figure 6.16 shows HCP benefit score responses for patients certified for terminal illness. Benefit ratings were provided on 11 of the completed surveys. Among the 11 responses, 3 reported no benefit and 2 reported the highest degree of benefit (score of 7); 8 (73%) reported a benefit score ≥ 4 on the seven-point scale.

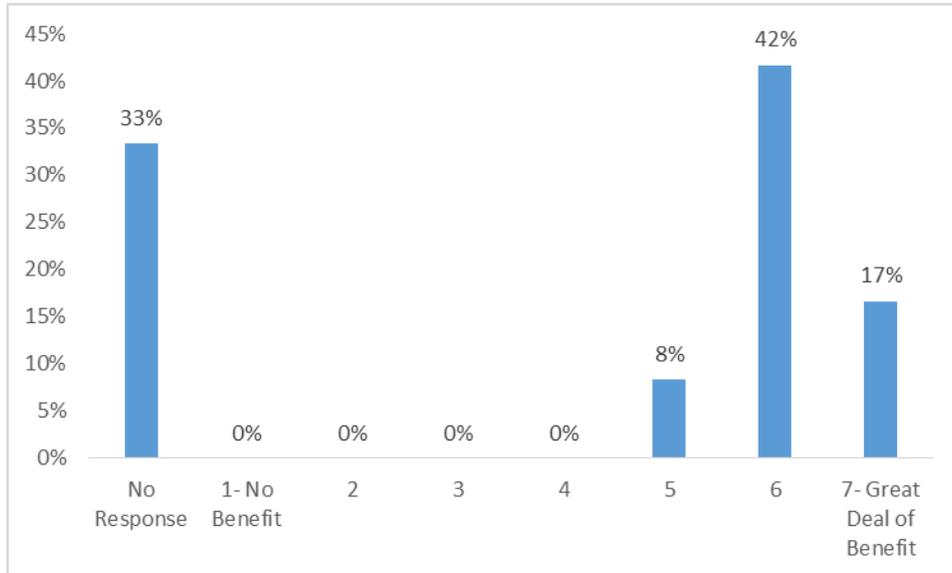
Figure 6.16. HCP-Perceived Benefit: Terminal Illness (N=12)



HIV/AIDS

Figure 6.17 shows HCP benefit score responses for patients certified for HIV/AIDS. Benefit ratings were provided on 8 of the 12 completed surveys. Among the 8 responses, none reported no benefit and two reported the highest degree of benefit (score of 7); all eight reported a benefit score ≥ 4 on the seven-point scale.

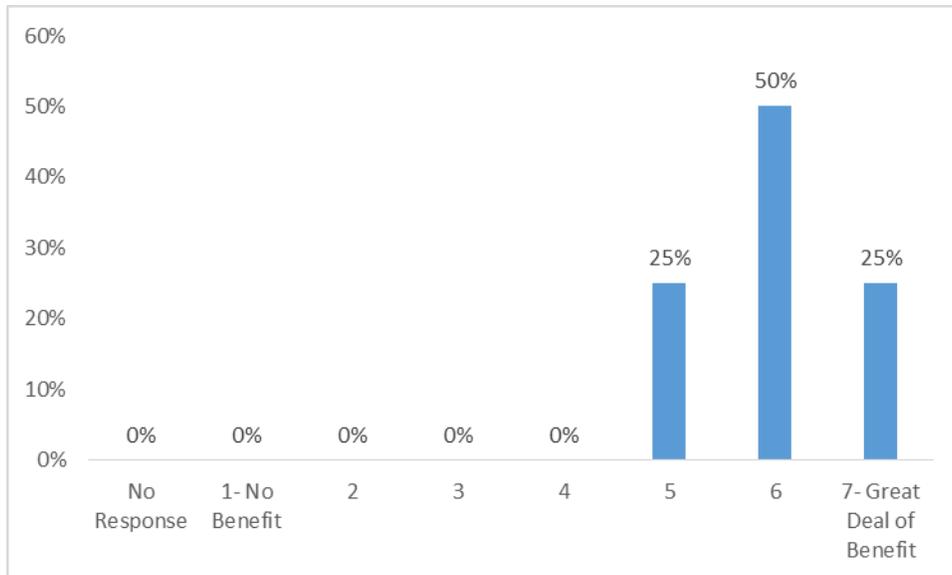
Figure 6.17. HCP-Perceived Benefit: HIV/AIDS (N=12)



TOURETTE SYNDROME

Figure 6.18 shows HCP benefit score responses for patients certified for Tourette syndrome. Benefit ratings were provided on all four of the completed surveys. Among the 4 responses, none reported no benefit and one reported the highest degree of benefit (score of 7); all four reported a benefit score ≥ 4 on the seven-point scale.

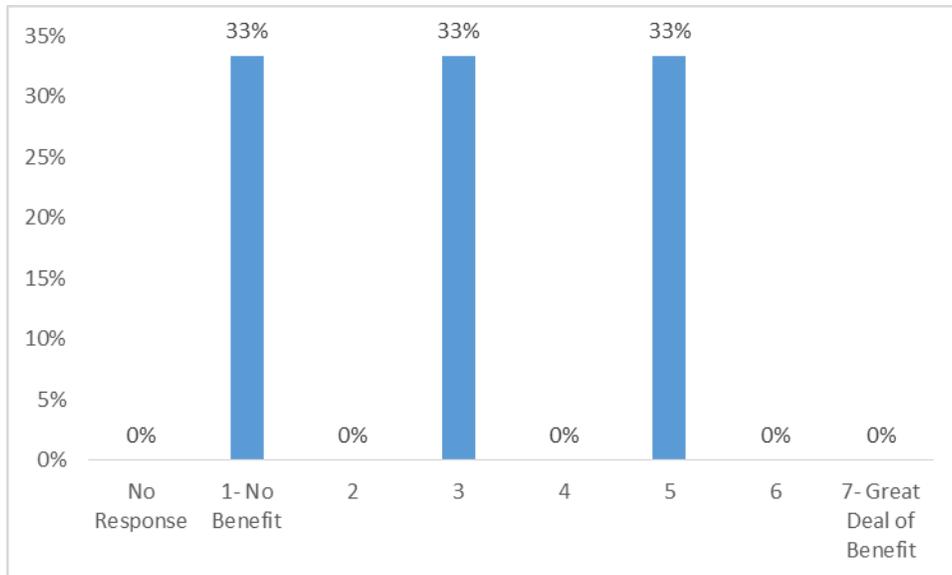
Figure 6.18. HCP-Perceived Benefit: Tourette Syndrome (N=4)



GLAUCOMA

Figure 6.19 shows HCP benefit score responses for patients certified for glaucoma. Benefit ratings were provided on all three of the completed surveys. Among the 3 responses, one reported no benefit and none reported the highest degree of benefit (score of 7); only one reported a benefit score ≥ 4 on the seven-point scale.

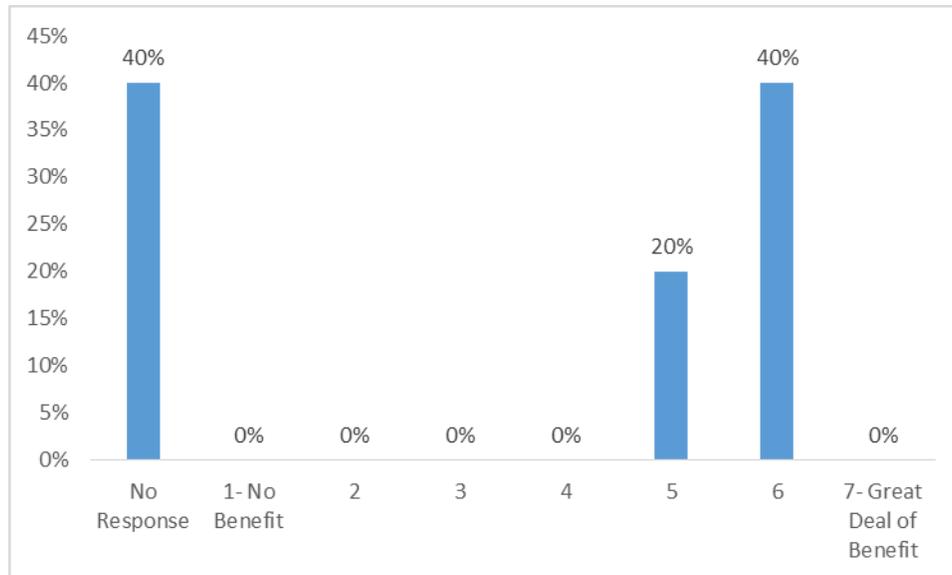
Figure 6.19. HCP-Perceived Benefit: Glaucoma (N=3)



ALS

Figure 6.20 shows HCP benefit score responses for patients certified for ALS. Benefit ratings were provided on 3 of the 5 completed surveys. Among the 3 responses, none reported no benefit and none reported the highest degree of benefit (score of 7); all three reported a benefit score ≥ 4 on the seven-point scale.

Figure 6.20. HCP-Perceived Benefit: ALS (N=5)



HCP Perceptions of Symptom Improvement from Medical Cannabis Treatment

Similar to the format in the Patient Experience survey, the HCP surveys asks certifying HCPs to describe the most significant benefit to the patient that is associated with medical cannabis treatment. Each response was reviewed and classified into broad categories of symptom improvement or global health benefits, as described in an earlier section. A full report of all benefit comments from HCPs can be found in *Appendix B: Healthcare Practitioner-Reported Benefits from Surveys*. Table 6 summarizes the reported “most important benefits” which could be considered improvement of a symptom related to the patient’s qualifying condition from reports of both patients and HCPs, again using a subset of patient responses from the same time window as HCP responses (surveys for patients making a first purchase between July 2015 and December 2015).

Table 6.11 Distribution of Symptom Improvement by Condition

Symptom Improvement by Score		1	2	3	4	5	6	7	Total
		(No Benefit)						(Great Deal of Benefit)	
Muscle Spasms									
Spasm Reduction	Patient (n=182)	-	-	-	6 (3%)	5 (3%)	14 (8%)	25 (14%)	50 (28%)
	HCP (n= 98)	-	-	1 (1%)	2 (2%)	6 (6%)	9 (9%)	9 (9%)	28 (29%)
Pain Reduction	Patient (n=182)	-	-	2 (1%)	3 (2%)	10 (6%)	10 (6%)	22 (12%)	47 (26%)
	HCP (n= 98)	-	1 (1%)	-	3 (3%)	4 (4%)	3 (3%)	11 (11%)	22 (22%)
Cancer									
Pain Reduction	Patient (n=84)	-	-	-	3 (4%)	7 (8%)	6 (7%)	7 (8%)	23 (27%)
	HCP (n= 51)	1 (2%)	-	2 (4%)	1 (2%)	2 (4%)	2 (4%)	2 (4%)	10 (20%)
Reduced Nausea/Vomiting	Patient (n=84)	-	-	-	1 (1%)	2 (2%)	1 (1%)	10 (12%)	14 (17%)

Symptom Improvement by Score		1	2	3	4	5	6	7	Total
		(No Benefit)						(Great Deal of Benefit)	
<i>Weight Gain/Appetite Improvement</i>	HCP (n= 51)	-	-	-	1 (2%)	5 (10%)	3 (6%)	4 (8%)	13 (26%)
	Patient (n=84)	-	-	-	-	1 (1%)	3 (4%)	7 (8%)	11 (13%)
	HCP (n= 51)	-	-	-	-	-	1 (2%)	-	1 (2%)
Seizures									
<i>Seizure Reduction</i>	Patient (n=120)	-	3 (3%)	1 (1%)	4 (3%)	11 (9%)	17 (14%)	31 (26%)	67 (56%)
	HCP (n= 64)	1 (2%)	2 (3%)	2 (3%)	2 (3%)	2 (3%)	5 (8%)	4 (6%)	18 (28%)
Crohn's Disease									
<i>Pain Reduction</i>	Patient (n=34)	-	-	-	-	2 (6%)	2 (6%)	4 (12%)	8 (24%)
	HCP (n= 25)	-	-	1 (4%)	-	-	3 (12%)	-	4 (16%)
<i>Reduced Gastrointestinal Symptoms</i>	Patient (n=34)	-	-	-	-	-	1 (3%)	4 (12%)	5 (15%)
	HCP (n= 25)	-	-	-	-	1 (4%)	-	1 (4%)	2 (8%)
<i>Weight Gain/Appetite Improvement</i>	Patient (n=34)	-	-	-	-	1 (3%)	1 (3%)	-	2 (9%)
	HCP (n= 25)	-	-	-	-	-	-	-	-
Terminal Illness									
<i>Reduced Nausea/Vomiting</i>	Patient (n=21)	-	-	-	1 (5%)	-	1 (5%)	4 (19%)	6 (29%)

Symptom Improvement by Score		1	2	3	4	5	6	7	Total
		(No Benefit)						(Great Deal of Benefit)	
<i>Pain Reduction</i>	HCP (n= 12)	-	-	-	-	1 (8%)	1 (8%)	1 (8%)	3 (25%)
	Patient (n=21)	-	-	-	1 (5%)	-	-	4 (19%)	5 (24%)
	HCP (n= 12)	-	-	-	-	1 (8%)	-	1 (8%)	2 (17%)
	Patient (n=21)	-	-	-	-	-	-	2 (10%)	2 (10%)
<i>Weight Gain/Appetite Improvement</i>	HCP (n= 12)	-	-	-	-	1 (8%)	1 (8%)	-	2 (17%)
	HIV/AIDS								
<i>Pain Reduction</i>	Patient (n=15)	-	-	1 (7%)	-	-	1 (7%)	3 (20%)	5 (33%)
	HCP (n= 12)	-	-	-	-	1 (8%)	1 (8%)	-	2 (17%)
<i>Reduced Nausea/Vomiting</i>	Patient (n=15)	-	-	-	-	-	-	3 (20%)	3 (20%)
	HCP (n= 12)	-	-	-	-	-	2 (17%)	-	2 (17%)
<i>Weight Gain/Appetite Improvement</i>	Patient (n=15)	-	-	-	-	-	-	2 (13%)	2 (13%)
	HCP (n= 12)	-	-	-	-	-	-	-	-
Tourette Syndrome									
<i>Reduced Tics/Tourette Symptoms</i>	Patient (n=6)	-	-	-	-	1 (17%)	-	3 (50%)	4 (67%)
	HCP (n= 5)	-	-	-	-	-	2 (40%)	1 (20%)	3 (60%)

Symptom Improvement by Score		1	2	3	4	5	6	7	Total
		(No Benefit)						(Great Deal of Benefit)	
Glaucoma									
<i>Reduced Glaucoma Symptoms</i>	Patient (n=5)	-	-	-	-	-	-	2 (40%)	2 (40%)
	HCP (n= 3)	-	-	1 (33%)	-	-	-	-	1 (33%)
ALS									
<i>Spasm Reduction</i>	Patient (n=7)	-	-	-	-	-	1 (14%)	-	1 (14%)
	HCP (n= 5)	-	-	-	-	1 (20%)	1 (20%)	-	2 (40%)
<i>Pain Reduction</i>	Patient (n=7)	-	-	-	-	-	1 (14%)	2 (29%)	3 (43%)
	HCP (n= 5)	-	-	-	-	-	1 (20%)	-	1 (20%)

Patients represented in Patient Experience survey responses and in HCP responses were different; thus a direct comparison cannot be made between the proportions of patients and HCPs reporting any given benefit. However, it is worth noting that relatively high levels of symptom improvement benefit (most scores are above 4) are seen in both patient and HCP survey results. Among patient respondents certified for muscle spasms, 22% report spasm reduction at a high degree of benefit (scores of 6 or 7) and 18% of HCP responses for patients with muscle spasms report spasm reduction at a high degree of benefit. Among responses of patients certified for seizures, 40% reported reduction in seizure number or severity at a high degree of benefit; among HCP responses for patients with seizures, 14% reported seizure reduction (severity or frequency) at a high degree of benefit. Among patient responders certified for cancer, 15% reported pain reduction at a high degree of benefit; 13% reported reduced nausea or vomiting at a high degree of benefit and 12% reported weight gain or appetite improvement at a high degree of benefit. Among HCP responses for patients certified for cancer, 8% reported pain reduction at a high degree of benefit, 14% reported reduced nausea or vomiting and 2% reported weight gain or appetite improvement at a high degree of benefit.

HCP Perceptions of Global Health Benefits from Medical Cannabis Treatment

Table 6.12 summarizes responses to the Patient Experience and HCP surveys about the most significant benefit to the patient that were not classified as improvement of symptoms related to the qualifying medical condition.

As with Table 6.11, the proportion of patients reporting a type of global health benefit cannot be directly compared to the proportion of HCPs reporting a type of global health benefit to the patient because each group of responders is different. However, in general a higher proportion of the patient responses report a global health benefit as the primary benefit from medical cannabis than HCP responses and generally global health benefits are reported at a relatively high degree of perceived benefit (scores of 4 or greater).

Overall, 1% of HCP respondents and 6% of patient respondents reported improved sleep as the most important benefit from medical cannabis; 3% of HCP respondents and 4% of patients reported improved quality of life; 2% of HCP reports and 3% of patient reports cited reduced usage of other medications or related side effects as the most important benefit.

A full report of all benefit comments from HCPs can be found in *Appendix B: Healthcare Practitioner-Reported Benefits from Surveys*.

Table 6.12 Distribution of Global Health Benefits by Condition

Global Health Benefits by Score		1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
Muscle Spasms									
<i>Improved Quality of Life</i>	Patient (n=182)	-	-	-	-	-	2 (1%)	3 (2%)	5 (3%)
	HCP (n= 98)	-	-	-	1 (1%)	1 (1%)	1 (1%)	1 (1%)	4 (4%)
<i>Improved Sleep</i>	Patient (n=182)	-	-	-	2 (1%)	3 (2%)	3 (2%)	6 (3%)	14 (8%)
	HCP (n= 98)	-	-	-	1 (1%)	-	-	1 (1%)	2 (2%)
<i>Improved Mobility/Ability to Function</i>	Patient (n=182)	-	1 (1%)	-	-	-	-	6 (3%)	7 (4%)
	HCP (n= 98)	-	-	-	-	-	-	-	-
<i>Decreased Anxiety</i>	Patient (n=182)	-	-	-	-	-	1 (1%)	2 (1%)	3 (2%)
	HCP (n= 98)	-	-	1 (1%)	-	-	-	-	1 (1%)

Global Health Benefits by Score		1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
<i>Reduced Usage of Other Medications</i>	Patient (n=182)	-	-	-	-	-	-	6 (3%)	6 (3%)
	HCP (n= 98)	-	-	-	-	-	1 (1%)	3 (3%)	4 (4%)
Cancer									
<i>Reduced Anxiety</i>	Patient (n=84)	-	-	-	1 (1%)	-	-	1 (1%)	2 (2%)
	HCP (n= 51)	-	-	-	-	-	-	-	-
<i>Improved Sleep</i>	Patient (n=84)	-	-	1 (1%)	-	1 (1%)	-	5 (6%)	7 (8%)
	HCP (n= 51)	-	-	-	-	-	-	-	-
<i>Improved Quality of Life</i>	Patient (n=84)	-	-	-	-	-	1 (1%)	1 (1%)	2 (2%)
	HCP (n= 51)	-	-	-	-	1 (2%)	-	-	1 (2%)
<i>Improved Alertness/Cognitive Functioning</i>	Patient (n=84)	-	-	-	-	-	-	1 (1%)	1 (1%)
	HCP (n= 51)	-	-	-	-	-	-	-	-
<i>Reduced Usage of Other Medications</i>	Patient (n=84)	-	-	-	-	-	1 (1%)	3 (4%)	4 (5%)
	HCP (n= 51)	-	-	-	-	-	-	-	-
Seizures									
<i>Improved Sleep</i>	Patient (n=120)	-	-	-	-	-	1 (1%)	-	1 (1%)
	HCP (n= 64)	-	-	-	-	-	-	-	-
<i>Reduced Usage of Other Medications</i>	Patient (n=120)	-	-	-	-	-	-	1 (1%)	1 (1%)
	HCP (n= 64)	-	-	-	-	-	-	-	-
<i>Improved Quality of Life</i>	Patient (n=120)	-	-	-	-	2 (2%)	1 (1%)	1 (1%)	4 (3%)
	HCP (n= 64)	-	-	-	1 (2%)	-	-	-	1 (2%)

Global Health Benefits by Score		1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
<i>Improved Alertness/Cognitive Functioning</i>	Patient (n=120)	-	2 (2%)	1 (1%)	3	2 (2%)	4 (8%)	1 (1%)	13 (11%)
	HCP (n= 64)	-	-	-	-	-	-	-	-
Crohn's Disease									
<i>Improved Quality of Life</i>	Patient (n=34)	-	-	-	-	-	-	4 (12%)	4 (12%)
	HCP (n= 25)	-	-	-	-	-	-	-	-
<i>Improved Sleep</i>	Patient (n=34)	-	-	1 (3%)	1 (3%)	1 (3%)	1 (3%)	-	4 (12%)
	HCP (n= 25)	-	-	-	1 (4%)	-	-	-	1 (4%)
<i>Decreased Anxiety</i>	Patient (n=34)	-	-	-	-	-	1 (3%)	-	1 (3%)
	HCP (n= 25)	-	-	-	-	-	1 (4%)	-	1 (4%)
Terminal Illness									
<i>Improved Alertness/ Cognitive Functioning</i>	Patient (n=21)	-	-	-	-	-	-	-	-
	HCP (n= 12)	-	-	-	-	-	-	1 (8%)	1 (8%)
<i>Improved Sleep</i>	Patient (n=21)	-	-	1 (5%)	-	-	-	2 (10%)	3 (14%)
	HCP (n= 12)	-	-	-	-	-	-	-	-
<i>Reduced Usage of Other Medications</i>	Patient (n=21)	-	-	-	-	-	-	-	-
	HCP (n= 12)	-	-	-	-	-	1 (8%)	-	1 (8%)
<i>Improved Quality of Life</i>	Patient (n=21)	-	-	-	-	-	1 (5%)	1 (5%)	2 (10%)
	HCP (n= 12)	-	-	-	-	-	-	-	-
HIV/AIDS									
<i>Improved Quality of Life</i>	Patient (n=15)	-	-	-	-	-	-	-	-

Global Health Benefits by Score		1 (No Benefit)	2	3	4	5	6	7 (Great Deal of Benefit)	Total
<i>Improved Sleep</i>	HCP (n= 12)	-	-	-	-	-	-	1 (8%)	1 (8%)
	Patient (n=15)	-	-	-	-	-	-	1 (7%)	1 (7%)
	HCP (n= 12)	-	-	-	-	-	-	-	-
	Patient (n=15)	-	-	-	-	-	-	-	-
<i>Decreased Anxiety</i>	HCP (n= 12)	-	-	-	-	-	1 (8%)	-	1 (8%)
Tourette Syndrome									
<i>Improved Quality of Life</i>	Patient (n=6)	-	-	-	-	-	-	1 (2%)	1 (2%)
	HCP (n= 5)	-	-	-	-	-	-	-	-
Glaucoma									
<i>Improved Sleep</i>	Patient (n=5)	-	-	-	-	-	-	-	-
	HCP (n= 3)	-	-	-	-	1 (33%)	-	-	1 (3%)
ALS									
<i>Reduced Anxiety</i>	Patient (n=7)	-	-	-	-	-	1 (14%)	1 (14%)	2 (29%)
	HCP (n= 5)	-	-	-	-	-	-	-	-

Additional Clinical Observations

Healthcare practitioners were asked to provide any additional clinical observations or insights on the impact of medical cannabis treatment on the patient’s condition, and were specifically prompted to report any observations on drug interactions. A third of the 114 observations describe a decrease in the patients’ other medications- mainly opioids and benzodiazepines. The survey healthcare practitioners will complete for patients certified for intractable pain will ask specifically about this issue. There were a few comments about drug interactions with anti-epileptic drugs, including in some cases the anticipated ability to decrease dose of Clobazam. A full report of these observations can be found in *Appendix C: Healthcare Practitioner-Reported Clinical Observations from Surveys*.

Patient Versus HCP Perceptions of Benefit from Medical Cannabis

Among survey respondents, there were 126 patients who submitted a survey for whom their certifying health care practitioner also completed a survey. Comparison of benefit scores reported by the patient to benefit scores reported by the healthcare practitioner are shown in Table 6.13, grouping scores of 1 or 2 in a category representing no or little benefit; scores of 3, 4, or 5 were grouped into a category representing mild or moderate benefit and scores of 6 or 7 were placed in a category representing strong benefit. Among these 126 patients and their HCPs, 81 (64%) of patient-HCP pairs were in general agreement regarding degree of benefits experienced: 46% reported strong benefit from medical cannabis; 15% reported mild or moderate benefit and 3% reported no or little benefit (Table 6.13). When interpreting the meaning of these comparisons, it must be kept in mind that the 126 patients for whom both Patient Experience and HCP survey results are available are not necessarily representative of all patients who enrolled in the program during its first year of operation.

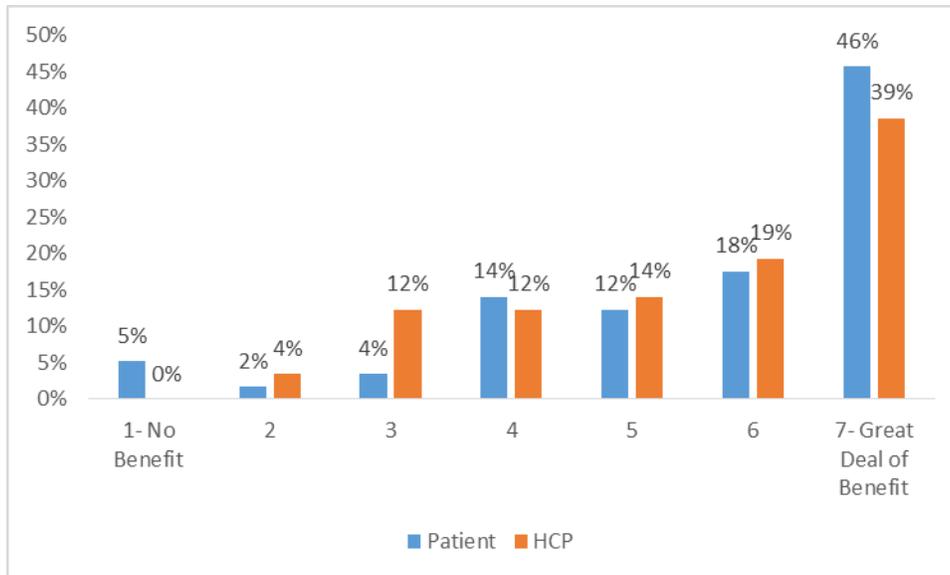
Table 6.13. Distribution of patient-reported benefits and HCP-reported benefits for patients with both patient and HCP surveys completed (n=126).

	HCP-Perceived Benefit		
Patient-Perceived Benefit	No/Little Benefit (1-2)	Mild/Moderate Benefit (3-5)	Strong Benefit (6-7)
No/Little Benefit (1-2)	4 (3%)	1 (1%)	2 (2%)
Mild/Moderate Benefit (3-5)	7 (6%)	19 (15%)	10 (8%)
Strong Benefit (6-7)	2 (2%)	23 (18%)	58 (46%)

Severe and Persistent Muscle Spasms

Figure 6.21 shows benefit scores reported by patients and their certifying HCPs for muscle spasms patients for whom both scores were available (n=57). Comparison of proportions of patients and HCPs reporting each benefit score shows fairly good agreement: 46% of patients and 39% of HCPs report scores of 6 or 7; 5% of patients and 0% HCPs report no benefit.

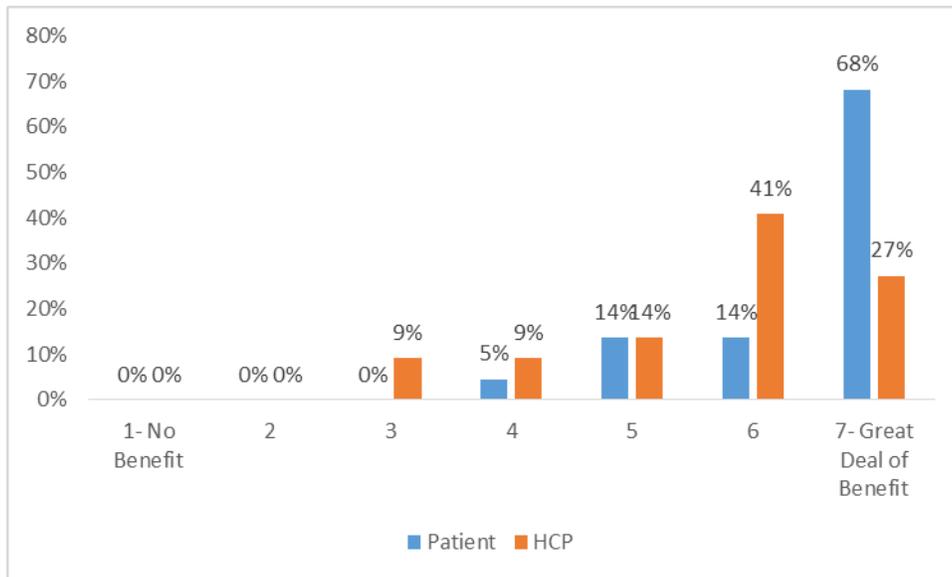
Figure 6.21. Muscle Spasms (N=57): Perceived Benefit



Cancer

Figure 6.22 shows benefit scores reported by patients and their certifying HCPs for cancer patients for whom both scores were available (n=22). Comparison of proportions of patients and HCPs reporting each benefit score shows differences in effect size but general agreement that patients experienced some benefit. Among this group, 68% of patients and 27% of HCPs report scores of 6 or 7; 0% patients and 0% HCPs report scores of 1 or 2.

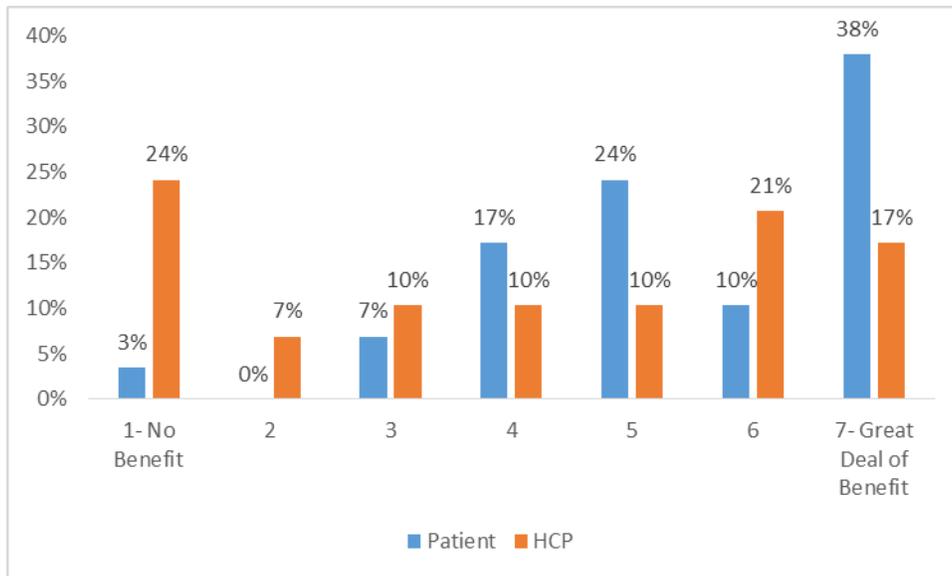
Figure 6.22. Cancer (N=22): Perceived Benefit



Seizures

Figure 6.23 shows benefit scores reported by patients and their certifying HCPs for seizure patients for whom both scores were available (n=29). Comparison of proportions of patients and HCPs reporting each benefit score shows that generally patients report higher degrees of benefit than HCPs: 38% of patients versus 17% of HCPs report scores of 6 or 7; 3% of patients versus 24% HCPs report no benefit.

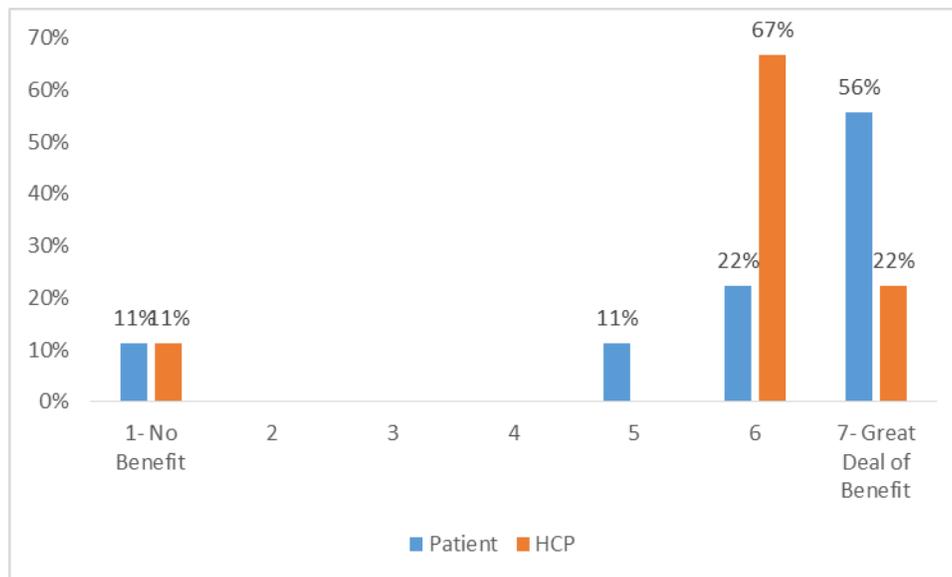
Figure 6.23. Seizures (N=29): Perceived Benefit



Crohn's Disease

Figure 6.24 shows benefit scores reported by patients and their certifying HCPs for Crohn's disease patients for whom both scores were available (n=9). Comparison of proportions of patients and HCPs reporting each benefit score shows general agreement about degree of benefit experienced: 89% of patients and 78% of HCPs report scores of 6 or 7; 11% of both patients and HCPs report scores of 1.

Figure 6.24. Crohn's Disease (N=9): Perceived Benefit



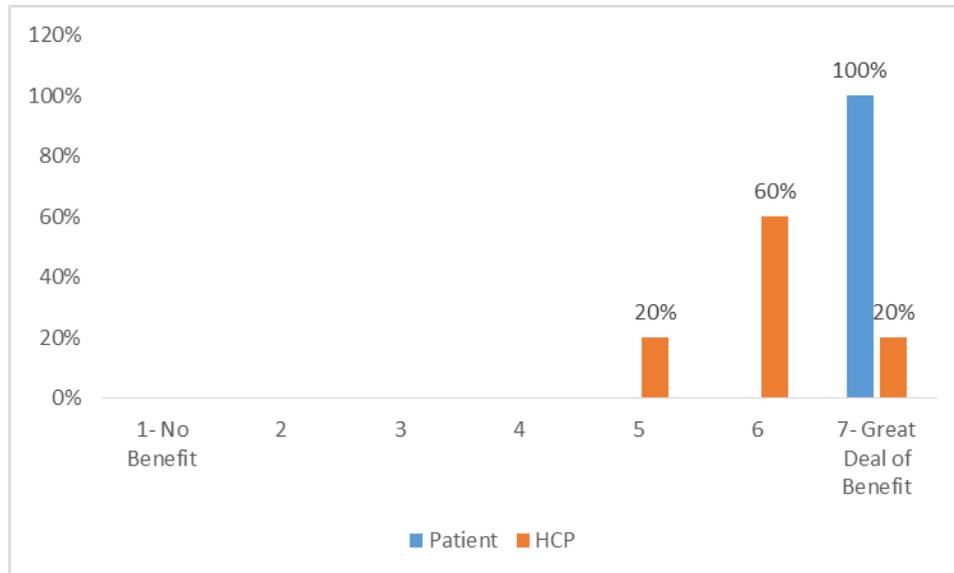
Terminal Illness

No patients with terminal illness had both an HCP-submitted survey and patient-submitted survey.

HIV/AIDS

Figure 6.25 shows benefit scores reported by patients and their certifying HCPs for HIV/AIDS patients for whom both scores were available (n=5). Comparison of proportions of patients and HCPs reporting each benefit score shows general agreement about degree of benefit experienced: 100% of patients and 80% of HCPs report scores of 6 or 7.

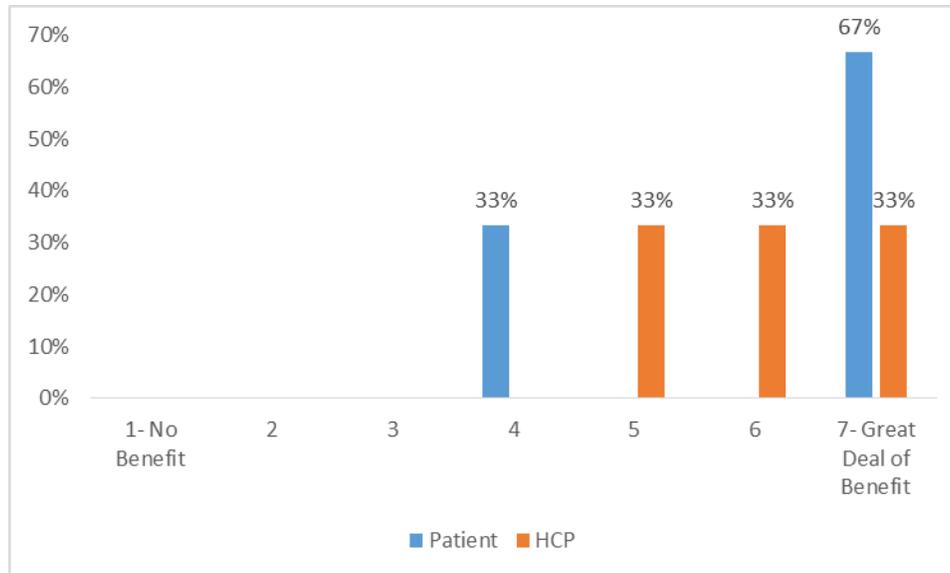
Figure 6.25. HIV/AIDS (N=5): Perceived Benefit



Tourette Syndrome

Figure 6.26 shows benefit scores reported by patients and their certifying HCPs for Tourette syndrome patients for whom both scores were available (n=3). Comparison of proportions of patients and HCPs reporting each benefit score shows general agreement about degree of benefit experienced: 67% of patients and 67% of HCPs report scores of 6 or 7.

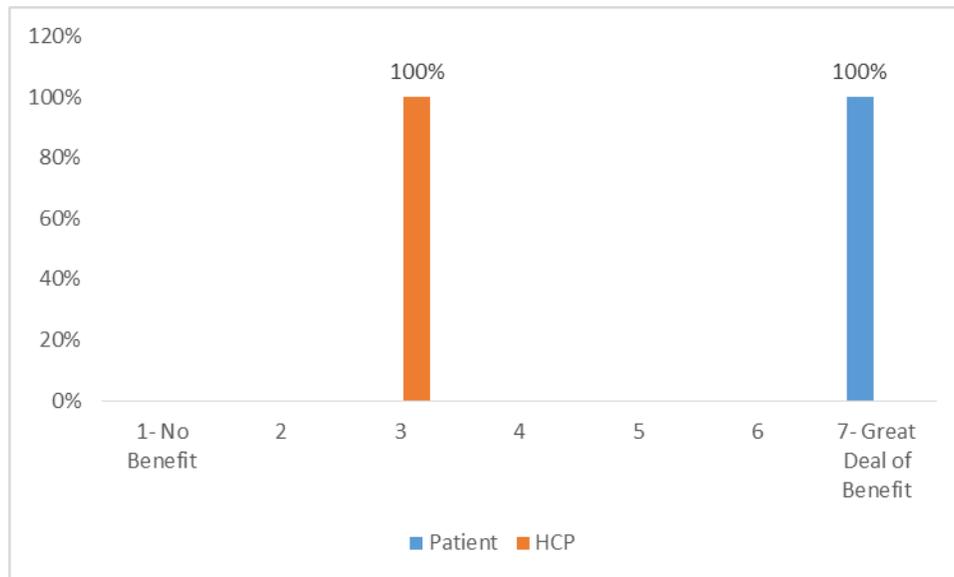
Figure 6.26. Tourette Syndrome (N=3): Perceived Benefit



Glaucoma

Figure 6.27 shows the benefit scores reported for one glaucoma patient who completed a survey (reported benefit score of 7) and whose HCP also completed a survey (reported benefit score of 3).

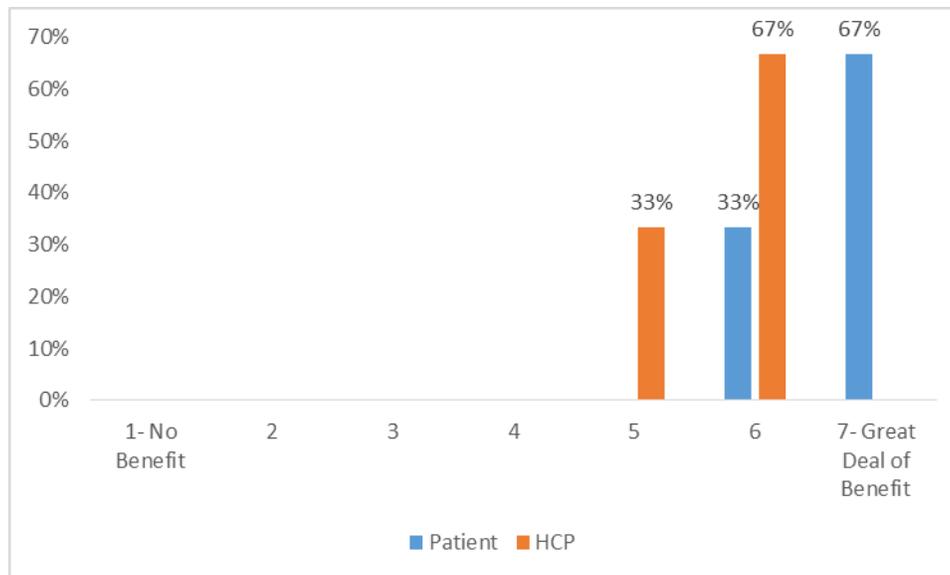
Figure 6.27. Glaucoma (N=1): Perceived Benefit



ALS

Figure 6.28 shows benefit scores reported by patients and their certifying HCPs for ALS patients for whom both scores were available (n=3). Comparison of proportions of patients and HCPs reporting each benefit score shows general agreement about degree of benefit experienced: 100% of patients and 67% of HCPs report scores of 6 or 7.

Figure 6.28. ALS (N=3): Perceived Benefit



Benefits Reported on Surveys: Conclusions

Of 1491 patients making a purchase in the first program year, 53% completed a survey three months after the first purchase. Among respondents, 43% reported experiencing the highest degree of benefit from medical cannabis and 87% reported at least a moderate degree of benefit (score of 4 or greater on a 1 to 7 scale). Patients reported the types of benefits experienced, which were predominantly (64%) various types of symptom improvement; many patients (25%) also reported global health benefits as the most important benefits from medical cannabis.

For patients making a purchase in the first six months of the program (n=774), 32% of HCP surveys were submitted. Overall, HCP reports of benefit were more conservative than those of patients, but 20% reported that the patient experienced the highest degree of benefit from medical cannabis and 60% reported at least a moderate degree of benefit. Among patients purchasing in the first six program months, 126 patients had both patient and HCP surveys completed and comparison of benefit scores indicated general agreement between the two scores for most patients.

Benefits Reported on the Patient Self-Evaluation

The Patient Self-Evaluation (PSE) contains questions that allow the Office of Medical Cannabis (OMC) to look for improvements in symptoms over time. Patients are required to complete a PSE prior to each medical cannabis purchase (including before their first medical cannabis purchase). This allows for capture of the patients’ symptoms at baseline – prior to taking any medical cannabis, as well as prior to each subsequent medical cannabis purchase. Hence, symptom change over time can be analyzed during the patients’ participation in the program.

All patients received a standard set of 8 symptom measures on the PSE. In addition, some patients received additional symptom questions depending on their qualifying medical condition(s). These two sets of symptom measures will be subsequently discussed below. Data from the PSE were extracted from patients who enrolled during the first program year (enrolled between July 1, 2015 and June 30, 2016; 1660 patients enrolled during this time period).

Standard 8 Symptom Measures

The standard 8 symptom measures that all patients received are answered on a 0-10 numerical rating scale (NRS), with 0 indicating absence of the symptom to 10 indicating that the symptom is as bad as the patient can imagine (see Box 6.1). Therefore, higher scores on these measures indicate poorer management of these symptoms. Patients are asked to rate symptom severity over the past 24 hours.

Box 6.1. Listing of the Standard 8 symptom measures that all patients answer, including the responses options available to patients.

<u>Standard 8 Symptom Measures:</u>											
Anxiety									Fatigue		
Lack of Appetite									Nausea		
Depression									Pain		
Disturbed Sleep									Vomiting		
<u>Response Options (0 – 10 NRS):</u>											
	0	1	2	3	4	5	6	7	8	9	10
Symptom not present											Symptom as bad as one can image

To understand whether patients derived any symptom benefits during their participation in the program, the following three questions were explored for each Standard 8 symptom measure:

QUESTION 1

Of those patients who experienced moderate to severe symptoms at baseline (score of 4 or higher at baseline), what percentage of them experienced at least a 30% improvement in symptoms within four months of their first medical cannabis purchase? The threshold of $\geq 30\%$ reduction on a 0-10 point scale was chosen because this threshold has been documented in clinical trials to represent clinically meaningful change – especially for pain reduction and spasticity reduction. Examples of $\geq 30\%$ change include moving from a score of 10 to a score of 7, from 9 to 6, from 8 to 5, from 7 to 4, etc.

QUESTION 2

If a patient achieved at least a 30% improvement on symptoms within 4 months of their first medical cannabis purchase (determined in Question 1), what percentage of them will, on average, still maintain that level of improvement in the four months following that initial 30% symptom improvement? [Four-month follow-up period]

QUESTION 3

What medical cannabis products were purchased just *prior* to the patient’s initial report of symptom improvement (first time patient indicated $\geq 30\%$ improvement on the PSE)? What was the average daily intake of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) for these product types?

To address Question 1 the following procedure was adopted for each standard 8 measure: all patients who scored 4 or higher at baseline were identified as those experiencing moderate to severe symptoms, and all standard 8 responses that were submitted within 4 months of their first medical cannabis purchase were retained. From this dataset, each patient’s standard 8 responses were compared to their baseline response over time. The first instance a patient achieved at least a 30% symptom improvement was recorded, effectively demonstrating when – during the first 4 months following their first medical cannabis purchase – the patient achieved symptom improvement, if at all.

Calculating the percentage of patients who achieved $\geq 30\%$ symptom improvement within 4 months of their first medical cannabis purchase (Question 1) was done in two ways. In one method, the number of patients who achieved $\geq 30\%$ symptom improvement within 4 months was divided by the total number of patients that ever made a first purchase (patients with baseline PSE data). In the other method, the number of patients achieving $\geq 30\%$ symptom improvement within 4 months was divided by patients who had submitted additional PSE data (beyond their baseline response) within 4 months of their first purchase. The denominator in

the former method includes all patients who made a first purchase (all patients with a baseline PSE submission), while the latter method effectively restricts the denominator to those patients who submitted additional PSE symptom data following their baseline submission and within 4 months of their first purchase. Therefore, the former method allows for a more conservative estimation of symptom benefit. In the text of this report, we present results using the former, more conservative estimate of benefit. Those who made no additional purchases after their first purchase may have discontinued use because of lack of effectiveness, though they may have discontinued use for other reasons as well (i.e., medical cannabis cost, side effects, etc.).

Since Question 1 examines symptom improvement within 4 months of their first medical cannabis purchase, patients who had not been enrolled in the program for at least 4 months since their first medical cannabis purchase were not included in the analysis. When PSE data were extracted in late December 2016, 1512 patients from the first year cohort (91.1% of the 1st year cohort) had been enrolled for at least 4 months since their first medical cannabis purchase—results on the standard 8 symptom measures are reported on this cohort subset.

Question 2 was addressed by observing all symptom responses in the four months *following* the time point when the patient first achieved $\geq 30\%$ symptom improvement. For each patient, all symptom responses identified during those follow-up four months were averaged together. Patients who, on average, still maintained at least a 30% symptom improvement from baseline were identified as those showing persistence in their symptom benefits.

For Question 3, products that were purchased just *prior* to each patient's initial $\geq 30\%$ symptom improvement were identified and categorized by their THC/CBD ratio and intended route of administration (ROA). See Box 6.2 for definitions of these categories.

Box 6.2. Categories to describe medical cannabis products purchased by patients.

Medical Cannabis Products Categorized by THC:CBD Content Ratio:

- **Very High THC to CBD** = 100:1 or higher
- **High THC to CBD** = >4:1 up to 99:1
- **Balanced** = 1:1 up to 4:1
- **High CBD to THC** = \geq 1:1 up to 99:1
- **Very High CBD to THC** = 100:1 or higher

Product Routes of Administration (ROA):

- **Enteral:** for absorption through the gastrointestinal tract (includes capsules and oral solutions to swallow).
- **Inhalation:** for absorption through the lungs (includes products for vaporization)
- **Oromucosal:** for absorption through the oral mucosa (includes sublingual sprays and tinctures to hold in the mouth)

Overall Results on Standard 8 Symptom Measures

Data on the Standard 8 symptom measures were first analyzed across all patients regardless of their qualifying condition(s) and are displayed in Table 6.14 (n = 1512). The third and fourth column respectively display the number and percentage of patients (out of 1512 patients) experiencing moderate to severe symptoms at baseline (baseline response \geq 4) on a given Standard 8 measure. With the exception of vomiting, the responses from patients indicated a high degree of burden on all symptom measures at baseline (~60-90% patients indicated moderate to severe symptoms).

The fifth column in Table 6.14 shows the percentage and number of patients (out of those reporting at moderate to severe levels at baseline) who had achieved at least a 30% symptom improvement at any time within 4 months of their first medical cannabis purchase. Anywhere from 36% to 60% of patients reported achieving at least a 30% improvement in symptoms within 4 months of their first medical cannabis purchase. Improvements in pain and fatigue were the least likely to reach \geq 30% improvement in patients (respectively at 36.3% and 40.2%), with the greatest proportion of patients reaching \geq 30% improvement in nausea (55.6%), depression (56.8%), and vomiting (60.2%).

The number of patients who had symptom data in the 4-month period *following* their initial \geq 30% symptom improvement are listed in the sixth column in Table 6.14. All symptom responses during this time period were averaged together within each patient. The seventh column shows the percentage and number of patients who had achieved \geq 30% symptom improvement that had – on average – maintained at least that level of improvement in the 4-

month follow-up period. Roughly a half to two-thirds of the patients who achieved at least 30% symptom improvement had maintained it in the following 4 months. Lastly, the right-most column shows the percentage of all patients who both achieved and maintained at least a 30% symptom improvement in the 4-month follow-up period. For the majority of all symptoms, roughly a third of all patients experiencing moderate to severe symptoms will both achieve and maintain at least a 30% improvement in symptoms for at least 4 months.

For a more detailed look on overall results from the eight standard symptom measures, please refer to *Appendix D: Symptom Results from the Patient Self-Evaluation*. This Appendix shows the following for each Standard 8 measure: 1) a figure showing the distribution of patient responses at baseline, 2) a figure showing the cumulative percentage of patients achieving at least 30% symptom improvement at 2 weeks, 1 month, 2 months, 3 months, and 4 months (the denominator is different between the orange and blue bars; orange bars include all moderate to severe scoring patients at baseline while blue bars restrict analyses to only those patients who submitted data by the time point indicated on the x-axis), and 3) a figure showing the frequency distribution of patients by the average symptom change (%) each patient experienced in the 4-month follow-up period since they initially achieved $\geq 30\%$ symptom reduction.

Table 6.14. Overall standard 8 symptom results.

Condition	Standard 8 Symptom Measure	# of Patients Reporting at Moderate to Severe Levels at Baseline	% of Patients Reporting at Moderate to Severe Levels at Baseline	% of Patients Achieving $\geq 30\%$ Symptom Improvement within 4 months of First Purchase out of all Moderate to Severe Baseline Scorers (n)	# of Patients with Data in 4-mo Period Following Initial $\geq 30\%$ Symptom Improvement	% of Patients Who Achieved $\geq 30\%$ Symptom Improvement that Maintained it for at Least 4 months (n)	% of Patients that Both Achieved $\geq 30\%$ Symptom Improvement and Retained that Degree of Improvement for at Least 4 months
All Patients - Collapsed Across Conditions (n = 1512)	Anxiety	1185	78.4	53.8 (638)	460	53.1 (339)	28.6
	Appetite Lack	963	63.7	53.7 (517)	383	57.1 (295)	30.6
	Depression	1000	66.1	56.8 (568)	419	56.7 (322)	32.2
	Disturbed Sleep	1323	87.5	50.3 (665)	519	52.0 (346)	26.2
	Fatigue	1381	91.3	40.2 (555)	415	48.6 (270)	19.6
	Nausea	864	57.1	55.6 (480)	362	59.2 (284)	32.9
	Pain	1312	86.8	36.3 (476)	329	45.0 (214)	16.3
	Vomiting	480	31.7	60.2 (289)	213	57.8 (167)	34.8

Results on Standard 8 Symptom Measures Stratified by Qualifying Condition

Data on the Standard 8 symptom measures were also analyzed separately by qualifying condition. Results are presented in Table 6.15 below. The first column indicates the qualifying condition and the total number of patients who had been enrolled in the program for at least 4 months since their first medical cannabis purchase. For some conditions, results are further broken down by condition subcategories (i.e., breakdown cancer patients based on whether their certifying condition was accompanied by pain, nausea/vomiting, etc.); condition subcategories are preceded by a star (*). The third and fourth columns in Table 6.15 indicate the number and percentage of patients who experienced moderate to severe symptoms (score ≥ 4) at baseline for each symptom.

The fifth column in Table 6.15 indicates the percentage and number of patients (out of those reporting at moderate to severe levels at baseline) that had achieved at least a 30% symptom improvement at any time within 4 months of their first medical cannabis purchase. The number of patients who had symptom data in the 4-month period *following* their initial $\geq 30\%$ symptom improvement are listed in the sixth column in Table 6.15. All symptom responses submitted during this time period were averaged together within each patient. The seventh column shows the percentage and number of patients that had achieved at least a 30% symptom improvement that had subsequently maintained it, on average, for at least 4 months. Lastly, the right-most column shows the percentage of all patients that had both achieved and maintained at least a 30% symptom improvement for at least 4 months.

Results generally show a high degree of burden for these eight symptoms at baseline. The instances where symptom severity is noticeably lower tend to be as expected; for example, nausea and vomiting in patients with Tourette syndrome and in patients with glaucoma. Among baseline responses to the eight symptom measures, those with the highest proportion rated as moderate to severe (score ≥ 4) include fatigue, disturbed sleep, pain, and anxiety. For each of the medical conditions, a substantial proportion of patients achieved $\geq 30\%$ reduction in most of the eight symptoms. Improvement was generally a bit higher in patients with seizures and with Tourette Syndrome and a bit lower in patients with cancer. Overall, a smaller proportion of patients achieved $\geq 30\%$ reduction of pain and fatigue and a higher proportion of patients achieved $\geq 30\%$ improvement in appetite and reduction in vomiting. For each medical condition, roughly half to three-quarters of the patients who experienced a $\geq 30\%$ reduction in a particular symptom within the first four months maintained that level of improvement over the following four months.

Table 6.15. Standard 8 symptom results stratified by qualifying condition.

Condition	Standard 8 Symptom Measure	# of Patients Reporting at Moderate to Severe Levels at Baseline	% of Patients Reporting at Moderate to Severe Levels at Baseline	% of Patients Achieving ≥30 Symptom Improvement within 4 months of First Purchase (n)	# of Patients with Data in 4-mo Period Following Initial ≥30% Symptom Improvement	% of Patients Who Achieved ≥30% Symptom Improvement that Maintained it for at Least 4 months (n)	% of Patients that Both Achieved ≥30% Symptom Improvement and Retained that Degree of Improvement for at Least 4 months
Muscle Spasms (n = 667)	Anxiety	553	82.9	54.8 (303)	250	60.7 (184)	33.3
	Appetite Lack	407	61.0	58.2 (237)	198	65.0 (154)	37.8
	Depression	471	70.6	58.0 (273)	227	63.0 (172)	36.5
	Disturbed Sleep	604	90.6	49.7 (300)	265	61.7 (185)	30.6
	Fatigue	624	93.6	42.0 (262)	227	55.3 (145)	23.2
	Nausea	366	54.9	63.1 (231)	195	65.4 (151)	41.3
	Pain	640	96.0	33.8 (216)	188	51.4 (111)	17.3
	Vomiting	192	28.8	65.1 (125)	103	66.4 (83)	43.2
Cancer (n = 405)	Anxiety	309	76.3	45.0 (139)	112	56.1 (78)	25.2
	Appetite Lack	321	79.3	39.3 (126)	102	57.1 (72)	22.4
	Depression	274	67.7	48.5 (133)	101	55.6 (74)	27.0
	Disturbed Sleep	355	87.7	42.0 (149)	122	47.0 (70)	19.7
	Fatigue	384	94.8	25.3 (97)	83	41.2 (40)	10.4
	Nausea	283	69.9	38.2 (108)	85	60.2 (65)	23.0
	Pain	356	87.9	28.9 (103)	80	40.8 (42)	11.8
	Vomiting	168	41.5	47.6 (80)	64	57.5 (46)	27.4
*Cancer: Pain (n = 285)	Pain	268	94.0	31.0 (83)	64	41.0 (34)	12.7
*Cancer: Nausea/Vomiting (n = 235)	Appetite Lack	200	85.1	41.0 (82)	66	57.3 (47)	23.5
	Nausea	184	78.3	34.8 (64)	49	54.7 (35)	19.0
	Vomiting	113	48.1	44.2 (50)	39	52.0 (26)	23.0
*Cancer: Cachexia/Wasting (n = 147)	Appetite Lack	124	84.4	38.7 (48)	39	58.3 (28)	22.6
Seizures (n = 299)	Anxiety	202	67.6	67.3 (136)	120	71.3 (97)	48.0
	Appetite Lack	145	48.5	76.6 (111)	97	73.9 (82)	56.6
	Depression	158	52.8	73.4 (116)	101	74.1 (86)	54.4
	Disturbed Sleep	242	80.9	69.0 (167)	155	63.5 (106)	43.8
	Fatigue	246	82.3	61.8 (152)	143	64.5 (98)	39.8
	Nausea	138	46.2	72.5 (100)	93	79.0 (79)	57.2
	Pain	190	63.5	60.0 (114)	106	69.3 (79)	41.6
	Vomiting	90	30.1	80.0 (72)	66	79.2 (57)	63.3

Table 6.15 Continued. Standard 8 symptom measures.

Condition	Standard 8 Symptom Measure	# of Patients Reporting at Moderate to Severe Levels at Baseline	% of Patients Reporting at Moderate to Severe Levels at Baseline	% of Patients Achieving ≥30 Symptom Improvement within 4 months of First Purchase (n)	# of Patients with Data in 4-mo Period Following Initial ≥30% Symptom Improvement	% of Patients Who Achieved ≥30% Symptom Improvement that Maintained it for at Least 4 months (n)	% of Patients that Both Achieved ≥30% Symptom Improvement and Retained that Degree of Improvement for at Least 4 months
Crohn's Disease (n = 102)	Anxiety	87	85.3	57.5 (50)	43	54.0 (27)	31.0
	Appetite Lack	80	78.4	53.8 (43)	37	58.1 (25)	31.3
	Depression	68	66.7	51.5 (35)	31	65.7 (23)	33.8
	Disturbed Sleep	89	87.3	42.7 (38)	37	65.8 (25)	28.1
	Fatigue	96	94.1	36.5 (35)	31	48.6 (17)	17.7
	Nausea	72	70.6	65.3 (47)	31	59.6 (28)	38.9
	Pain	97	95.1	41.2 (40)	32	47.5 (19)	19.6
	Vomiting	31	30.4	54.8 (17)	16	82.4 (14)	45.2
Terminal Illness (n = 81)	Anxiety	60	74.1	51.7 (31)	28	58.1 (18)	30.0
	Appetite Lack	64	79.0	37.5 (24)	19	45.8 (11)	17.2
	Depression	54	66.7	48.1 (26)	22	61.5 (16)	29.6
	Disturbed Sleep	65	80.2	44.6 (29)	28	55.2 (16)	24.6
	Fatigue	76	93.8	21.1 (16)	14	37.5 (6)	7.9
	Nausea	56	69.1	44.6 (25)	23	64.0 (16)	28.6
	Pain	72	88.9	19.4 (14)	11	50.0 (7)	9.7
	Vomiting	35	43.2	57.1 (20)	18	50.0 (10)	28.6
*Terminal Illness: Pain (n = 57)	Pain	54	94.7	20.4 (11)	8	45.5 (5)	9.3
*Terminal Illness: Nausea/Vomiting (n = 36)	Appetite Lack	31	86.1	41.9 (13)	11	61.5 (8)	25.8
	Nausea	28	77.8	35.7 (10)	10	70.0 (7)	25.0
	Vomiting	18	50.0	50.0 (9)	8	44.4 (4)	22.2
*Terminal Illness: Cachexia/Wasting (n = 29)	Appetite Lack	23	79.3	43.5 (10)	9	60.0 (6)	26.1
HIV/AIDS (n = 48)	Anxiety	44	91.7	50.0 (22)	20	68.2 (15)	34.1
	Appetite Lack	39	81.3	48.7 (19)	17	63.2 (12)	30.8
	Depression	34	70.8	47.1 (16)	15	75.0 (12)	35.3
	Disturbed Sleep	44	91.7	50.0 (22)	18	50.0 (11)	25.0
	Fatigue	41	85.4	46.3 (19)	15	47.4 (9)	22.0
	Nausea	33	68.8	60.6 (20)	17	65.0 (13)	39.4
	Pain	45	93.8	40.0 (18)	14	50.0 (9)	20.0
	Vomiting	20	41.7	50.0 (10)	9	80.0 (8)	40.0

Table 6.15 Continued. Standard 8 symptom measures.

Condition	Standard 8 Symptom Measure	# of Patients Reporting at Moderate to Severe Levels at Baseline	% of Patients Reporting at Moderate to Severe Levels at Baseline	% of Patients Achieving ≥30 Symptom Improvement within 4 months of First Purchase (n)	# of Patients with Data in 4-mo Period Following Initial ≥30% Symptom Improvement	% of Patients Who Achieved ≥30% Symptom Improvement that Maintained it for at Least 4 months (n)	% of Patients that Both Achieved ≥30% Symptom Improvement and Retained that Degree of Improvement for at Least 4 months
Tourette Syndrome (n = 28)	Anxiety	26	92.9	69.2 (18)	17	72.2 (13)	50.0
	Appetite Lack	8	28.6	50.0 (4)	3	75.0 (3)	37.5
	Depression	20	71.4	75.0 (15)	14	86.7 (13)	65.0
	Disturbed Sleep	21	75.0	76.2 (16)	16	75.0 (12)	57.1
	Fatigue	21	75.0	66.7 (14)	13	50.0 (7)	33.3
	Nausea	5	17.9	100.0 (5)	5	80.0 (4)	80.0
	Pain	17	60.7	64.7 (11)	11	90.9 (10)	58.8
	Vomiting	1	3.6	100.0 (1)	1	100.0 (1)	100.0
Glaucoma (n = 21)	Anxiety	14	66.7	42.9 (6)	6	50.0 (3)	21.4
	Appetite Lack	7	33.3	85.7 (6)	5	66.7 (4)	57.1
	Depression	14	66.7	85.7 (12)	11	58.3 (7)	50.0
	Disturbed Sleep	18	85.7	61.1 (11)	10	54.5 (6)	33.3
	Fatigue	19	90.5	42.1 (8)	7	37.5 (3)	15.8
	Nausea	6	28.6	16.7 (1)	1	100.0 (1)	16.7
	Pain	18	85.7	33.3 (6)	6	50.0 (3)	16.7
	Vomiting	1	4.8	0.0 (0)	0	-- (0)	0.0
ALS (n = 21)	Anxiety	17	81.0	52.9 (9)	7	55.6 (5)	29.4
	Appetite Lack	8	38.1	87.5 (7)	5	57.1 (4)	50.0
	Depression	15	71.4	40.0 (6)	5	50.0 (3)	20.0
	Disturbed Sleep	18	85.7	33.3 (6)	6	83.3 (5)	27.8
	Fatigue	20	95.2	35.0 (7)	7	71.4 (5)	25.0
	Nausea	9	42.9	55.6 (5)	4	80.0 (4)	44.4
	Pain	17	81.0	47.1 (8)	7	25.0 (2)	11.8
	Vomiting	2	9.5	50.0 (1)	1	100.0 (1)	50.0

Appendix D: Symptom Results from the Patient Self-Evaluation shows the following for each Standard 8 measure stratified by qualifying medical condition: 1) a figure showing the distribution of patient responses at baseline, 2) a figure showing the cumulative percentage of patients achieving at least 30% symptom improvement at 2 weeks, 1 month, 2 months, 3 months, and 4 months (the denominator is different between the orange and blue bars; orange bars include all moderate to severe scoring patients at baseline while blue bars restrict analyses to only those patients who submitted data by the time point indicated on the x-axis), 3) a figure showing the frequency distribution of patients by the average symptom change (%) each patient experienced in the 4-month follow-up period since they initially achieved $\geq 30\%$ symptom reduction, and 4) a table of medical cannabis products patients purchased just prior to achieving $\geq 30\%$ symptom improvement for the first time, along with the average daily THC and CBD dose taken by patients.

Medical cannabis products that were purchased just prior to the initial 30% symptom improvement are discussed only briefly in this section (Question 3), and the reader is encouraged to see *Appendix D: Symptom Results from the Patient Self-Evaluation* for the full table of results. Here, only a few results regarding medical cannabis purchases are discussed as examples—some in relation to improvements on a particular Standard 8 measure, and others in relation to a particular condition-specific symptom measure.

Table 6.16 below shows the most common medical cannabis products that were purchased by cancer patients just prior to achieving the initial 30% reduction in nausea symptoms. The second column from the right indicates the number of patients who purchased specific products just prior to that initial symptom reduction (products purchased indicated by “X”s). The table also shows the average daily amount of THC and CBD (mg) patients consumed (right-most column), which was derived from manufacturer-supplied product information and pharmacist-entered calculations of how long the purchased supply would last. Very High THC:CBD vaporization products were purchased most frequently (n = 20), followed by a combination of Very High THC:CBD enteral products and Very High THC:CBD vaporization products (n = 12). See *Appendix D: Symptom Results from the Patient Self-Evaluation* for full results.

Table 6.16. Top 5 medical cannabis product(s) purchased by cancer patients just prior to achieving the initial 30% reduction in the Standard 8 nausea measure.

Very High THC to CBD	Enteral				Inhalation				Oromucosal				% of Patients out of 109 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)		
	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	High THC to CBD	High THC to CBD	Balanced			High CBD to THC	Very High CBD to THC
					X										18.3 (20)	55.9 mg/0.4 mg
X					X										11.0 (12)	71.6 mg/0.5 mg
										X					8.3 (9)	86.3 mg/0.4 mg
		X													6.4 (7)	135.5 mg/83.2 mg
X		X			X			X							4.6 (5)	61.4 mg/15.6 mg

Table 6.17 below shows the most common medical cannabis products that were purchased by terminal illness patients just prior to achieving the initial 30% reduction in nausea symptoms. The most frequently purchased products were a combination of both Very High THC:CBD products for oral administration and vaporization (n = 3), followed by Balanced THC:CBD products for inhalation only (n = 3). See *Appendix D: Symptom Results from the Patient Self-Evaluation* for full results.

Table 6.17. Top 7 medical cannabis product(s) purchased by terminal illness patients just prior to achieving the initial 30% reduction in the Standard 8 nausea measure.

Enteral			Inhalation			Oromucosal			% of Patients out of 26 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	Very High CBD to THC	High CBD to THC	Balanced	Very High THC to CBD	High THC to CBD	Balanced		
X						X			11.5 (3)	67.1 mg/0.5 mg
						X			11.5 (3)	44.5 mg/0.4 mg
X		X				X			7.7 (2)	45.5 mg/37.5 mg
		X			X				7.7 (2)	110.1 mg/5.9 mg
		X						X	7.7 (2)	78.6 mg/61.1 mg
		X							7.7 (2)	49.0 mg/46.0 mg
			X						7.7 (2)	4.4 mg/206.7 mg

Table 6.18 below shows the most common medical cannabis products purchased by HIV/AIDS patients just prior to their initial 30% reduction in pain symptoms. Balanced THC:CBD products were purchased most frequently (n = 6), followed by Very High THC:CBD products for inhalation (n = 3). See *Appendix D: Symptom Results from the Patient Self-Evaluation* for full results.

Table 6.18. Top 4 medical cannabis product(s) purchased by HIV/AIDS patients just prior to achieving the initial 30% reduction in the Standard 8 pain measure.

Enteral			Inhalation			Oromucosal			% of Patients out of 18 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	Very High CBD to THC	High CBD to THC	Balanced	Very High THC to CBD	High THC to CBD	Balanced		
		X							33.3 (6)	23.1 mg/22.1 mg
			X						16.7 (3)	65.2 mg/0.3 mg
X		X							11.1 (2)	5.0 mg/0.0 mg
			X		X				11.1 (2)	51.7 mg/18.2 mg

Condition-Specific Symptom Measures

In addition to the Standard 8 measures, some patients received additional symptom questions on the PSE to more adequately address condition-specific symptoms. These include, among others, questions on seizure frequency for seizure patients, questions on spasm frequency for muscle spasm and ALS patients, and Crohn’s activity in Crohn’s patients. While patients received the same response options on the Standard 8 measures (respond from 1-10 on a

numerical rating scale), response options for condition-specific measures varied and will be described in this section. All condition-specific measures were investigated within the same framework as the Standard 8 measures: 1) what percentage of patients achieved symptom improvement within the four months since their first medical cannabis purchase compared to their baseline responses, 2) what percentage of those achieving symptom improvement showed general persistence in the 4-month follow-up period, and 3) what medical cannabis products were purchased just prior to the patient reporting initial symptom improvements. A summary of results are similarly presented in a table like those presented for the Standard 8 measures (see Table 6.19 below).

The first column in Table 6.19 lists each condition that received additional symptom questions beyond the Standard 8. The second column briefly indicates the nature of these additional condition-specific symptom measures, with the number of patients included in the analysis at baseline indicated in the third column (baseline, meaning patients who provided data and met criteria on these measures at the beginning of the program – prior to purchasing any medical cannabis). The fourth column indicates the percentage and number of patients achieving a specified threshold of symptom improvement within four months of purchasing their first medical cannabis (denominator is patients included in the analysis at baseline). The threshold to determine symptom improvement for these analyses are subsequently described below, found in the descriptive section for each condition. The number of patients who had symptom data in the 4-month period following their initial symptom improvement are listed in the fifth column in Table 6.19. All symptom responses during this time period were averaged together within each patient. The sixth column indicates the percentage and number of patients who had achieved symptom improvement that subsequently still maintained that improvement for at least 4 months. Lastly, the right-most column shows the percentage of all patients who both achieved and maintained symptom improvements for at least 4 months. A more detailed discussion of these condition-specific results will follow Table 6.19.

Table 6.19. Condition-Specific Measures.

Condition	Condition-Specific Symptom Measure	# of Patients Included in Analysis	% of Patients Achieving Threshold Symptom Improvement within 4 months of First Purchase (n)	# of Patients with Data in 4-mo Period Following Initial Threshold Symptom Improvement	% of Patients Who Achieved Threshold Symptom Improvement that Maintained it for at Least 4 months (n)	% of Patients that Both Achieved Threshold Symptom Improvement and Retained that Degree of Improvement for at Least 4 months
Muscle Spasms	Weekly Spasms Frequency	629	48.0 (302)	225	57.6 (174)	27.6
	0-10 Spasticity Scale	618	36.4 (225)	197	47.1 (106)	17.2
Cancer: Nausea/Vomiting	Chemo-Induced Nausea	147	37.4 (55)	29	34.5 (19)	12.9
	Chemo-Induced Vomiting	77	41.6 (32)	20	56.3 (18)	23.4
Cancer: Cachexia/Wasting	Weight	147	13.6 (20)	15	45.0 (9)	6.1
Seizures	Weekly Seizure Frequency	262	68.3 (179)	150	70.9 (127)	48.5
Crohn's Disease	# Liquid Stools	41	51.2 (21)	17	57.1 (12)	29.3
	Abdominal Pain	73	53.4 (39)	29	35.9 (14)	19.2
	General Well-Being	15	46.7 (7)	5	28.6 (2)	13.3
	Measures Combined	102	51.0 (52)	41	42.3 (22)	21.6
	Weight	102	20.6 (21)	18	57.1 (12)	11.8
Terminal Illness: Cachexia/Wasting	Weight	29	20.7 (6)	5	50.0 (3)	10.3
HIV/AIDS	Weight	48	14.6 (7)	3	42.9 (3)	6.3
Tourette Syndrome	Weekly Tic Frequency	28	60.7 (17)	15	76.5 (13)	46.4
ALS	Weekly Spasms Frequency	18	33.3 (6)	4	66.7 (4)	22.2
	0-10 Spasticity Scale	15	20.0 (3)	3	100.0 (3)	20.0

Severe and Persistent Muscle Spasms

Patients with muscle spasms were given two questions to assess the severity of their muscle spasms. First, patients were given the option to respond to the number of muscle spasms they experienced the day before or the number of muscle spasms they experienced within the last week. These allowed for the calculation of weekly spasm frequency. Secondly, patients were asked to rate the severity of their muscle spasms on a 0-10 numerical rating scale (NRS), with 0 indicating absence of spasms to 10 indicating spasticity being as bad as the patient could imagine. For the analysis in Table 6.19 above, responses to the 0-10 spasticity measure were restricted to patients experiencing moderate to severe spasticity at baseline (score of 4 or higher), while all patients responding to the weekly spasms frequency question were included in the analysis. In the analysis of both measures, symptom improvement was defined as achieving at least a 30% reduction in symptoms (30% decrease in weekly spasm frequency; 30% decrease on the 0-10 NRS spasticity measure) compared to baseline.

Weekly spasm frequency was reduced by $\geq 30\%$ in nearly half (48.0%) of the muscle spasm patients. Among patients who achieved $\geq 30\%$ reduction, 58% (27.6% of patients included in analysis at baseline) retained that level of improvement over the next four months.

Severity of muscle spasticity was reduced by $\geq 30\%$ for 36.4% of the patients with moderate to severe muscle spasticity at baseline. Among patients who achieved $\geq 30\%$ reduction, 47% (17.2% of patients included in analysis at baseline) retained that level of improvement over the next four months.

Table 6.20 below shows the top 5 medical cannabis product types that were purchased by muscle spasm patients just prior to achieving $\geq 30\%$ weekly spasm reduction for the first time, including the number of patients who purchased those specific product types (second column from right). It also shows the average daily amount of THC and CBD (mg) patients consumed (right-most column), which was derived from manufacturer-derived product information and pharmacist-entered calculations of how long the purchased supply would last. Full purchasing details are in *Appendix D: Symptom Results from the Patient Self-Evaluation*. The most frequently purchased product types preceding the initial symptom improvement were a combination of Balanced THC:CBD products for oral administration and Balanced THC:CBD products for vaporization (n = 34), followed by Very High THC:CBD products for vaporization (n = 30).

Table 6.20. Top 5 medical cannabis product types purchased by muscle spasm patients just prior to achieving $\geq 30\%$ reduction in weekly spasms. Last column shows the average daily THC/CBD dose that was used by patients purchasing those product types (second column from right).

Enteral					Inhalation					Oromucosal					% of Patients out of 301 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
		X					X								11.3 (34)	55.3 mg/35.1 mg
					X										10.0 (30)	77.8 mg/0.5 mg
		X			X										9.6 (29)	79.6 mg/30.0 mg
		X													8.3 (25)	23.6 mg/22.4 mg
					X		X								7.0 (21)	99.8 mg/17.5 mg

Cancer: Nausea and Vomiting

Patients certified for cancer accompanied by severe and persistent nausea or vomiting were asked to assess the severity of chemotherapy-induced nausea and vomiting on a 0-10 numerical rating scale. Patients who experienced chemotherapy-induced nausea and vomiting at moderate to severe levels at baseline (score of 4 or higher) were included in the analysis in Table 6.19, with symptom improvement being defined as achieving at least a 30% improvement in symptoms (30% decrease on the 0-10 nausea/vomiting NRS) compared to baseline.

Severity of chemotherapy-induced nausea was reduced by $\geq 30\%$ for 37.4% of the patients with moderate to severe chemotherapy-induced nausea at baseline. Among the patients who achieved $\geq 30\%$ reduction, 35% (12.9% of patients included in analysis at baseline) retained that level of improvement over the next four months.

Severity of chemotherapy-induced vomiting was reduced by $\geq 30\%$ for 41.6% of the patients with moderate to severe chemotherapy-induced vomiting at baseline. Among the patients who achieved $\geq 30\%$ reduction, 56% (23.4% of patients included in analysis at baseline) retained that level of improvement over the next four months.

Cancer: Cachexia and Severe Wasting

Body weights were analyzed for patients certified for cancer accompanied by cachexia and/or severe wasting. Symptom improvement was defined as achieving at least a 3% increase in body weight compared to baseline weight.

An increase of at least 3% in body weight was reported by 13.6% of patients. Among the patients who achieved $\geq 3\%$ increase in body weight, 45% (6.1% of patients included in analysis at baseline) retained that increase over the next four months.

Seizures

Patients with seizures were given two questions to assess the severity of their seizures. First, patients were given the option to respond to the number of seizures they experienced the day before or the number of seizures they experienced within the last week. These allowed for the calculation of weekly spasm frequency. Table 6.19 shows results from the weekly seizure frequency measure, with symptom improvement defined as achieving at least a 30% improvement in symptoms (30% decrease in weekly seizure frequency) compared to baseline.

Weekly seizure frequency was reduced by $\geq 30\%$ in 68.3% of the seizure patients. Among patients who achieved $\geq 30\%$ reduction, 71% (48.5% of patients included in analysis at baseline) retained that level of improvement over the next four months.

Table 6.21 below shows the top 5 medical cannabis product types that were purchased by seizure patients just prior to achieving $\geq 30\%$ symptom improvement for the first time, including the number of patients who purchased those specific product types (second column from right). It also shows the average daily amount of THC and CBD (mg) patients consumed (right-most column), which was derived from manufacturer-derived product information and pharmacist-entered calculations of how long the purchased supply would last. Full purchasing details are in *Appendix D: Symptom Results from the Patient Self-Evaluation*. The most frequently purchased product types preceding the initial symptom improvement were skewed towards relatively high CBD:THC products, with preference for oral administration of these products.

Table 6.21. Top 5 medical cannabis product types purchased by seizure patients just prior to achieving ≥30% reduction in weekly seizures. Last column shows the average daily THC/CBD dose that was used by patients purchasing those product types (second column from right).

Enteral				Inhalation				Oromucosal				% of Patients out of 178 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
		X										48.3 (86)	7.6 mg/159.5 mg
										X		16.9 (30)	13.2 mg/407.4 mg
	X				X							4.5 (8)	56.0 mg/37.4 mg
		X	X									3.4 (6)	4.9 mg/282.5 mg
	X											2.8 (5)	19.3 mg/15.9 mg

Crohn's Disease

Three questions from the Harvey-Bradshaw Index (HBI), which measures Crohn's disease activity, were included on the PSE for Crohn's disease patients. These three questions addressed the following: 1) the number of liquid or soft stools experienced yesterday, 2) general well-being yesterday (response options: "Very well", "Slightly below par", "Poor", "Very poor", "Terrible"), and 3) abdominal pain yesterday (response options: "None", "Mild", "Moderate", "Severe"). Responses to these three questions were summed into a combined score for each patient (combined according to HBI scoring guidelines) as well as analyzed separately in Table 6.19. The three questions were selected from the HBI because they were patient-reported measures (versus clinician assessments). The HBI has been validated, but since only three questions from the HBI were used, the clinical significance of these aggregate and individual scores is unclear. Lastly, body weight data submitted through the PSE were analyzed and included in Table 6.19.

Patients who indicated they experienced five or more liquid/soft stools at baseline were included in the analysis, with symptom improvement defined as achieving at least a 30% reduction in liquid/soft stools. Patients who indicated their general well-being was "Very Poor" or "Terrible" at baseline were included in the well-being analysis, with symptom improvement defined as feeling "Slightly Below Par" or "Very Well". Patients who indicated they experienced "Moderate" or "Severe" abdominal pains were included in the abdominal pain analysis, with symptom improvement defined as experiencing "Mild" to "No" abdominal pain. For the combined Crohn's activity measure (combined score on the three HBI measures), symptom improvement was defined as those achieving at least a 30% symptom improvement (30% decrease in the combined score compared to baseline). Lastly, body weight improvement was defined as a 3% increase in body weight.

Number of liquid/soft stools per day decreased by $\geq 30\%$ for 51.2% of patients with at least five liquid/soft stools per day at baseline. Among patients who achieved $\geq 30\%$ reduction, 57% (29.3% of patients included in analysis at baseline) retained that level of improvement over the next four months.

Severity of abdominal pain improved for 53.4% of patients with moderate or severe abdominal pain at baseline. Among patients who reported an improvement in abdominal pain, 36% (19.2% of patients included in analysis at baseline) retained that improvement over the next four months.

General well-being improved for 46.7% of patients who described their baseline well-being as "Very Poor" or "Terrible" at baseline. Among patients who reported an improvement in general well-being, 29% (13.3% of patients included in analysis at baseline) retained that improvement over the next four months.

On the combined Crohn's activity measure (number of liquid/soft stools, abdominal pain, general well-being), 51.0% of Crohn's Disease patients achieved $\geq 30\%$ improvement. Among

patients who achieved $\geq 30\%$ reduction, 42% (21.6% of patients included in analysis at baseline) retained that level of improvement over the next four months.

An increase of at least 3% in body weight was reported by 20.6% of patients. Among the patients who achieved $\geq 3\%$ increase in body weight, 57% (11.8% of patients included in analysis at baseline) retained that increase over the next four months.

Terminal Illness

Body weight measures on the PSE were analyzed in patients certified for terminal illness: accompanied by cachexia or severe wasting. Symptom improvement was defined as a 3% increase in body weight from their baseline body weight.

An increase of at least 3% in body weight was reported by 20.7% of patients. Among the patients who achieved $\geq 3\%$ increase in body weight, 50% (10.3% of patients included in analysis at baseline) retained that increase over the next four months.

HIV/AIDS

Body weight measures on the PSE were analyzed in HIV/AIDS patients. Similar to all body weight measures of improvement discussed previously, symptom improvement was defined as a 3% increase in body weight compared to their baseline body weight.

An increase of at least 3% in body weight was reported by 14.6% of patients. Among the patients who achieved $\geq 3\%$ increase in body weight, 43% (6.3% of patients included in analysis at baseline) retained that increase over the next four months.

Tourette Syndrome

Patients with Tourette Syndrome were given two questions to assess the severity of their tics. First, patients were given the option to respond to the number of tics they experienced the day before or the number of tics they experienced within the last week. These allowed for the calculation of weekly tic frequency. For Table 6.19, weekly tic frequency was analyzed in all patients, with symptom improvement defined as a 30% improvement in symptoms (30% decrease in weekly tics compared to baseline).

Weekly tic frequency was reduced by $\geq 30\%$ in 60.7% of the Tourette Syndrome patients. Among patients who achieved $\geq 30\%$ reduction, 76% (46.4% of patients included in analysis at baseline) retained that level of improvement over the next four months.

Table 6.22 below shows the top 4 medical cannabis product types that were purchased by Tourette patients just prior to achieving $\geq 30\%$ symptom improvement for the first time, including the number of patients who purchased those specific product types (second column from right). It also shows the average daily amount of THC and CBD (mg) patients consumed (right-most column), which was derived from manufacturer-derived product information and pharmacist-entered calculations of how long the purchased supply would last. Full purchasing details are in *Appendix D: Symptom Results from the Patient Self-Evaluation*. The most frequently purchased product types preceding the initial symptom improvement were Very High THC:CBD oromucosal products (4 patients) and a combination of Balanced THC:CBD oral products and Very High THC:CBD oral products (2 patients)

Table 6.22. Top 4 medical cannabis product types purchased by Tourette patients just prior to achieving $\geq 30\%$ reduction in weekly tics. Last column shows the average daily THC/CBD dose that was used by patients purchasing those product types (second column from right).

Enteral			Inhalation			Oromucosal			% of Patients out of 17 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	Balanced	High CBD to THC	Very High THC to CBD	Balanced	High CBD to THC	Very High THC to CBD	Balanced	High CBD to THC		
						X			23.5 (4)	147.3 mg/0.7 mg
X	X								11.8 (2)	24.0 mg/15.0 mg
	X								11.8 (2)	11.5 mg/8.5 mg
			X						11.8 (2)	64.6 mg/0.2 mg

Glaucoma

Intraocular pressure results were collected on the PSE from Glaucoma patients and are presented in Table 6.23 for each of the 21 patients included in this analysis. At the first PSE (prior to first medical cannabis purchase) patients were asked to provide the date and results of the most recent intraocular pressure test. On subsequent PSEs patients were asked to provide the date and results of any intraocular pressure test done since submission of the last PSE.

Results for seven of the 21 patients (33%) suggest a decrease in intraocular pressure after initiation of medical cannabis: patients #4, 8, 9, 14, 16, 17, and 19. One of those seven did not show a decrease at 5 months, but did show a decrease at 9 months. Four of them had measurement results after the date of the result that indicated a decrease: patients #4, 16, 17, and 19. Of those four, three have results indicating persistence of reduction over several months. The fourth (#19) had a reduction in month 2 but returned toward pre-medical cannabis levels at month 4. More detailed study, including accessing medical record data, would be needed to confirm measurement results and to assess whether observed improvements could have been due to changes in glaucoma therapy other than medical cannabis use.

Table 6.23. Intraocular pressure test results (left eye/right eye) from glaucoma patients (n = 21). Test results are noted by the month they occurred prior to or after the patients' first medical cannabis purchase ("First Visit").

Patient	Before 1st Medical Cannabis Purchase							First Visit	After 1st Medical Cannabis Purchase										
	12-mo	11-mo	5-mo	4-mo	3-mo	2-mo	1-mo		1-mo	2-mo	3-mo	4-mo	5-mo	6-mo	7-mo	9-mo	10-mo	11-mo	13-mo
1		15 / 11											11 / 10		7 / 12				
2							20 / 17			17 / 14							18 / 16		
3							18 / 20		19 / 18			18 / 18	19 / 22	19 / 18					
4						26 / 28	26 / 28			18 / 18			18 / 16						
5							21 / 26												
6			20 / 20						20 / 20										
7							17 / 15												
8					34 / 30								33 / 33			26 / 24			
9							26 / 23		17 / 18										
10						30 / 30													
11			22 / 24	27 / 21	21 / 24														
12							12 / 10				12 / 12								
13							22 / 14		22 / 14										
14							9 / 26			8 / 12									
15						17 / 18			19 / 24										
16		22 / 20							16 / 16		17 / 17	16 / 16						18 / 19	
17							23 / 23		16 / 16	19 / 25		16 / 19	16 / 19			16 / 18			
18					10 / 12					12 / 15									
19							30 / 22			19 / 16		26 / 16							
20						17 / 19	19 / 17		19 / 17										
21							17 / 26		17 / 28		20 / 25				19 / 20				24 / 28

ALS

Patients with ALS were given two questions to assess the severity of their muscle spasms. First, patients were given the option to respond to the number of spasms they experienced the day before or the number of spasms they experienced within the last week. These allowed for the calculation of weekly spasm frequency. Table 6.19 presents results on weekly spasm frequency and spasm severity (0-10 NRS). For the spasticity scale measure, patients who experienced moderate to severe spasms at baseline (scored 4 or higher) were included in the analysis, with symptom improvement defined as achieving at least a 30% symptom improvement (30% decrease on the 0-10 NRS compared to baseline).

Weekly spasm frequency was reduced by $\geq 30\%$ in 33.3% of the ALS patients. Among patients who achieved $\geq 30\%$ reduction, 67% (22.2% of patients included in analysis at baseline) retained that level of improvement over the next four months.

Severity of muscle spasticity was reduced by $\geq 30\%$ for 20.0% of the ALS patients with moderate to severe muscle spasticity at baseline. Among the three patients who achieved $\geq 30\%$ reduction, all three retained that level of improvement over the next four months (20.0% of patients included in analysis at baseline).

Table 6.24 below shows the top 5 medical cannabis product types that were purchased by ALS patients just prior to achieving $\geq 30\%$ weekly spasm reduction for the first time, including the number of patients who purchased those specific product types (second column from right). It also shows the average daily amount of THC and CBD (mg) patients consumed (right-most column), which was derived from manufacturer-derived product information and pharmacist-entered calculations of how long the purchased supply would last. Full purchasing details are in *Appendix D: Symptom Results from the Patient Self-Evaluation*. The most frequently purchased product types preceding the initial symptom improvement were skewed towards balanced THC:CBD products and relatively high THC:CBD products.

Table 6.24. Top 5 medical cannabis product types purchased by ALS patients just prior to achieving $\geq 30\%$ reduction in weekly spasms. Last column shows the average daily THC/CBD dose that was used by patients purchasing those product types (second column from right).

Enteral			Inhalation			% of Patients out of 6 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
Very High THC to CBD	High THC to CBD	Balanced	Very High THC to CBD	High THC to CBD	Balanced		
		X				33.3 (2)	12.8 mg/5.1 mg
X			X			16.7 (1)	59.8 mg/0.3 mg
	X	X	X		X	16.7 (1)	67.0 mg/6.0 mg
	X	X				16.7 (1)	37.5 mg/8.1 mg
			X			16.7 (1)	42.2 mg/0.3 mg

Benefits Reported on the Patient Self-Evaluation: Conclusions

Similar to survey results, the PSE also demonstrated improvements on symptoms in medical cannabis patients. Patients enrolling in the program initially report a high degree of symptom burden with anywhere from roughly 40-60% of patients reporting symptom improvements within the 4 month period following their first medical cannabis purchase. If patients experienced improvements in symptoms, roughly half to three-quarters of them maintained those levels of improvement in the 4-month period following their initial report of improvement.

There are some limitations on the PSE to consider when interpreting results. Firstly, there is no symptom data on patients who decide over time not to purchase medical cannabis any longer (or for extended periods of time). As discussed earlier, patients must complete a PSE prior to each medical cannabis purchase. If a patient stops purchasing medical cannabis, there will be a parallel pause in symptom data to understand whether there may have been a lack of symptom improvements to halt purchases. This is the reason for presenting many analyses on symptom improvements in the context of the initial baseline patient pool – regardless of whether they provided any subsequent symptom data or not. This allows for more of a conservative estimate of symptom benefit over time. A second limitation on the PSE has to do with the patient’s approach and conscientiousness in completing the PSE—all symptom measures are self-reported which involves cognitive resources and motivation for the patient to complete the surveys as accurately as possible.

7. Adverse Side Effects

Summary

This chapter provides insight into the frequency and severity of adverse (negative) side effects through three sources of information: the Patient Self-Evaluation completed by the patient prior to each medical cannabis purchase, patient and health care practitioner surveys, and adverse event reports to the two medical cannabis manufacturers.

The three information sources tell a similar story. Around 20-25% of enrolled patients report negative physical or mental side effects of some kind, with the majority – around 60% - reporting only one and 90% reporting 3 or fewer unique side effects. The vast majority of adverse side effects, around 90%, are mild to moderate in severity. An assessment of the 30 patients reporting severe side effects, meaning “interrupts usual daily activities,” found no apparent pattern in patient age, medical condition, or type of medical cannabis product used. Results reported in this chapter are generally similar to those reported in published clinical trials of cannabis and cannabinoids, though with a somewhat lower frequency of occurrence reported in the program. Fortunately, up to the present no serious adverse events (life threatening or requiring hospitalization) have been reported.

Some limitations of the data should be mentioned. For example, when the patient completes a Patient Self-Evaluation and has it reviewed in consultation with pharmacist staff, the completeness and accuracy of reported side effects (on the Patient Self-Evaluation) ultimately depend on the attention and good communication of the patient. Perhaps a more significant risk for under-reporting through Patient Self-Evaluation data is the situation when a patient has an intolerable side effect and decides to make no more purchases of medical cannabis. If the patient doesn't go to a cannabis patient center for another purchase, the patient doesn't fill out another Patient Self-Evaluation, so the side effect is not documented through this mechanism. From anecdotal report and survey responses, we know this does occur. However, inquiries made of patients who have discontinued medical cannabis purchasing suggests this does not happen often. Finally, a weakness of the survey data is that many responders did not complete the question on most significant negative effect and a substantial proportion who did indicated cost or access issues, rather than physical or mental side effects. Though physical or mental side effects were probably minor or not present if the respondent indicated cost or access issues as the most significant negative effect, we don't know that for sure. We are unable to characterize most significant negative effect for those who did not submit a response.

Though the limitations mentioned in the paragraph above no doubt undercount the frequency of physical and mental side effects to some degree, their impact does not seem likely to

significantly change the main conclusions of the analyses reported in this section: at this point, the safety profile of the medical cannabis products available through the Minnesota program seems quite favorable.

Adverse Side Effects Reported on the Patient Self-Evaluation

Patients have the opportunity to report adverse side effects they attribute to medical cannabis on the Patient Self-Evaluation (PSE). Patients must complete a PSE prior to each medical cannabis purchasing transaction. Therefore, the administration of the PSE is timed so that patients can reflect on their experience with the medication they purchased previously and report those experiences on the following patient self-evaluation. A pharmacist at one of the eight medical cannabis dispensaries can then review PSE-reported information, which includes an opportunity to discuss side effects with the patient prior to approving that patient for another medical cannabis purchase. When reporting side effects on the PSE, patients are able to choose side effects from a pre-made list of options or write in side effects that do not fit one of the listed options. In addition, patients also indicate the severity with which each side effect is experienced (see Box 7.1).

Box 7.1. Definitions on severity provided to patients for adverse side effect reporting.

Adverse side effects were examined within the 1st program year cohort (n = 1660). Patients who had made at least their first medical cannabis purchase were identified, and from these patients, all PSEs that were

Adverse Side Effect Severity: Definitions

Mild: Symptoms do not interfere with daily activities

Moderate: Symptoms may interfere with daily activities

Severe: Symptoms interrupt usual daily activities

submitted within the four months following their first medical cannabis purchase were included in a dataset. This led to a total of 1502 patients (90.5% of the cohort) being represented. For the following analyses, each side effect was counted once for a given patient if it was reported multiple times. If a side effect was reported multiple times, the observation that was categorized at the highest severity level was included in the analyses for this report. In cases where a patient opted to write in their side effects (rather than choosing from the pre-made list of options), their responses were assessed carefully for adjudication for coding purposes. Therefore – while not affecting a substantial number of side effect responses – it should be noted that one limitation for accurate coding is the patient’s ability to adequately articulate their experiences.

Of the 1502 patients, 18.1% (n = 272) reported any adverse side effects within the four month period following their first medical cannabis purchase. Of those 272 patients reporting any adverse side effects, the majority reported only one (n = 164, 60.3%), with approximately 90% of them reporting three or fewer different, adverse side effects (Figure 7.1).

Figure 7.1. Distribution of patient counts by number of different, adverse side effects reported (out of 272 patients).

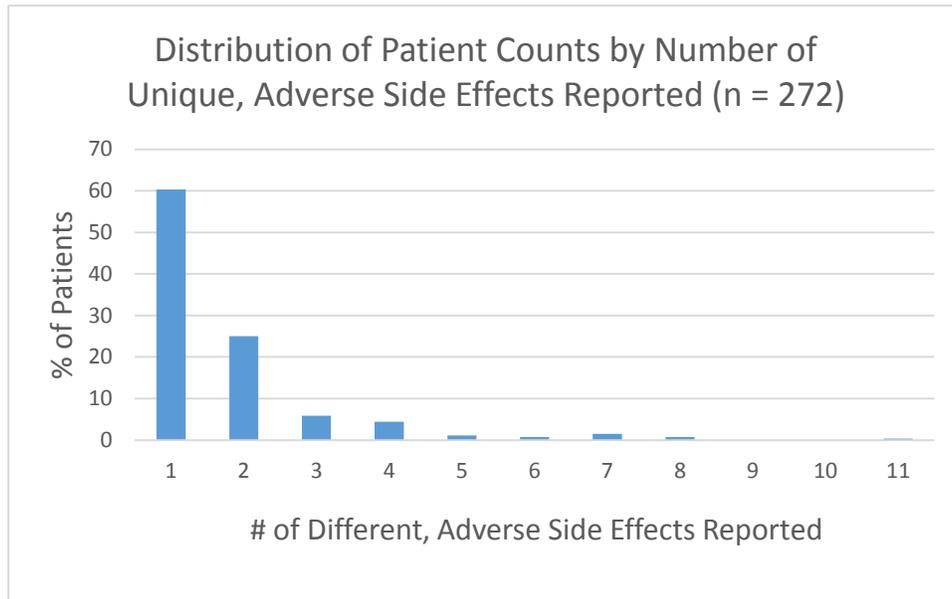


Figure 7.2 shows the percentage of patients reporting specific adverse side effects (Table 7.1 below lists adverse side effects that were reported by less than 2% of all patients). Of all side effects reported, dry mouth and drowsiness/somnolence/sedation were the most commonly reported side effects among patients. Overall, the frequency distribution of unique side effects mirrors typical clinical trial data on side effects from cannabis/cannabinoid use (see [“A Review of Medical Cannabis Studies relating to Chemical Compositions and Dosages for Qualifying Medical Conditions”](#) on the [Office of Medical Cannabis](#) website).

Figure 7.2. The most commonly reported adverse side effects represented by the percentage of patients reporting them (out of 272 patients).

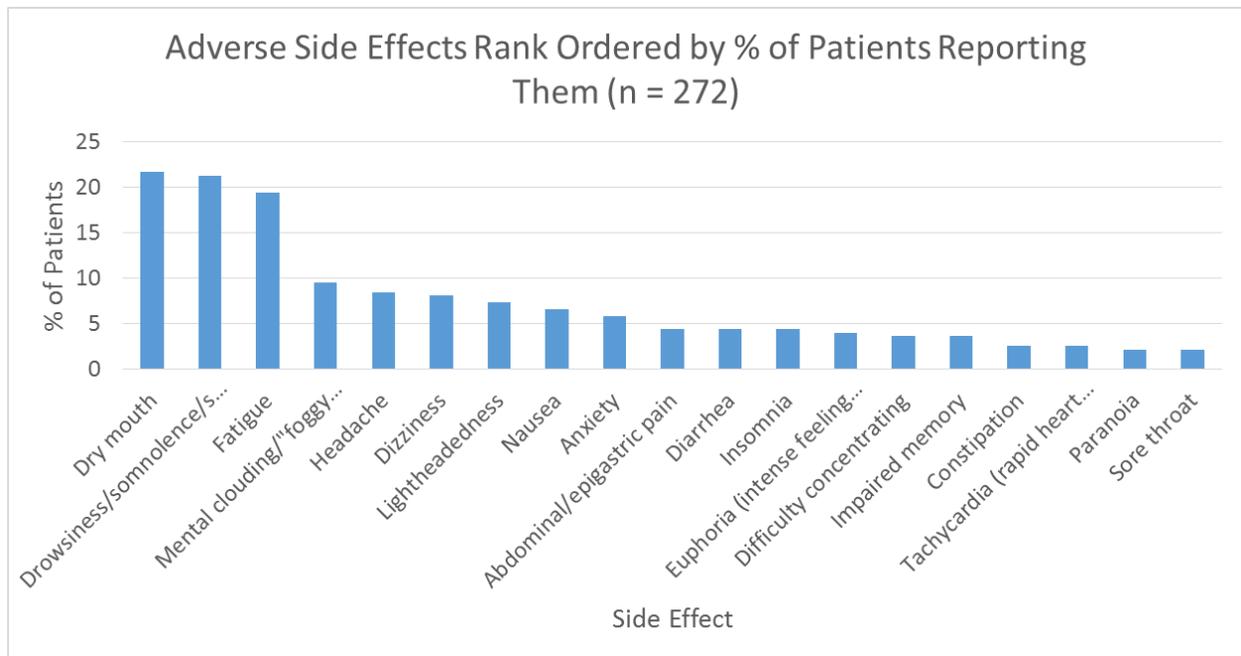


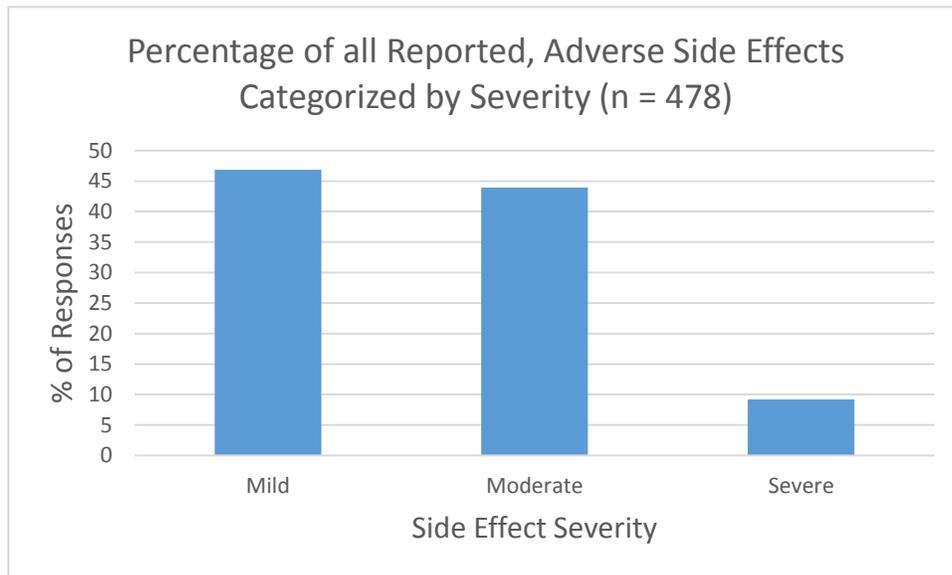
Table 7.1. Adverse side effects that were reported by less than 2% of patients (out of 272 patients).

Side Effect	% of Patients (n)
Asthenia (muscle weakness)	1.8% (5)
Chest pain	1.8% (5)
Confusion	1.8% (5)
Disorientation	1.5% (4)
Eye redness	1.5% (4)
Lethargy	1.5% (4)
Blurred Vision	1.1% (3)
Decreased muscle coordination/balance	1.1% (3)
Increased agitation	1.1% (3)
Numbness	1.1% (3)
Panic attack	1.1% (3)
Personality/mood change	1.1% (3)
Tinnitus (ringing perception in the ears)	1.1% (3)
"Stoned" feeling	0.7% (2)
Body stiffness	0.7% (2)
Coughing/lung irritation	0.7% (2)
Decreased appetite	0.7% (2)
Dry eyes	0.7% (2)
Feeling cold	0.7% (2)
Increased seizures	0.7% (2)
Tremors	0.7% (2)
"Wired" feeling	0.4% (1)
Bloating	0.4% (1)
Burping	0.4% (1)

Side Effect	% of Patients (n)
Change in quality of seizures	0.4% (1)
Chest colds	0.4% (1)
Cognitive change	0.4% (1)
Cramping with bowel movement	0.4% (1)
Dysphoria (intense feeling of unease or unpleasantness)	0.4% (1)
Exacerbation of lymphedema	0.4% (1)
Eye muscle twitching	0.4% (1)
Hives	0.4% (1)
Hyperactive bowel sounds	0.4% (1)
Hypomania	0.4% (1)
Increase in mucus secretions	0.4% (1)
Increased aggression	0.4% (1)
Increased urine output	0.4% (1)
Increased yelling	0.4% (1)
Mouth irritation/burning	0.4% (1)
Rash on face	0.4% (1)
Repressed immune system	0.4% (1)
Sleep disturbance	0.4% (1)
Sneezing	0.4% (1)
Thrush	0.4% (1)
Urinary retention	0.4% (1)
Vomiting	0.4% (1)
Worsening acne	0.4% (1)

The 272 patients reporting any adverse side effects submitted a combined total of 478 side effect responses within 4 months of their first medical cannabis purchase. When aggregating all side effect responses across patients, only 9.2% (44) of all responses were reported as severe (see Figure 7.3).

Figure 7.3. Percentage of all reported, adverse side effect responses categorized by severity.



Severe Adverse Side Effects

All adverse side effect responses that were categorized as severe are further broken down by the percent of patients categorizing them as such—please see Table 7.2 below.

Table 7.2. Table shows the number of patients reporting the listed side effects along with the percentage of those respondents who indicated that the side effect was severe.

Side Effect	# of Patients Reporting	% of Patients Reporting as Severe (n)
Dry mouth	59	6.8% (4)
Drowsiness/somnolence/sedation	58	5.2% (3)
Fatigue	53	3.8% (2)
Mental clouding/"foggy brain"	26	7.7% (2)
Headache	23	4.3% (1)
Dizziness	22	9.1% (2)
Lightheadedness	20	0% (0)
Nausea	18	11.1% (2)
Anxiety	16	12.5% (2)
Abdominal/epigastric pain	12	8.3% (1)
Diarrhea	12	16.7% (2)
Insomnia	12	8.3% (1)
Euphoria (intense feeling of well-being or pleasure)	11	9.1% (1)
Difficulty concentrating	10	20% (2)
Impaired memory	10	10% (1)
Constipation	7	14.3% (1)
Tachycardia (rapid heart rate)	7	28.6% (2)
Paranoia	6	16.7% (1)
Sore throat	6	0% (0)
Asthenia (muscle weakness)	5	60% (3)
Chest pain	5	20% (1)
Confusion	5	0% (0)
Disorientation	4	0% (0)
Eye redness	4	0% (0)
Lethargy	4	50% (2)
Blurred Vision	3	0% (0)
Decreased muscle coordination/balance	3	33.3% (1)
Increased agitation	3	0% (0)
Numbness	3	33.3% (1)
Panic attack	3	33.3% (1)
Personality/mood change	3	0% (0)
Tinnitus (ringing perception in the ears)	3	0% (0)
"Stoned" feeling	2	50% (1)
Body stiffness	2	0% (0)

Table 7.2 Continued. Table shows the number of patients reporting the listed side effects along with the percentage of those respondents who indicated that the side effect was severe.

Side Effect	# of Patients Reporting	% of Patients Reporting as Severe (n)
Coughing/lung irritation	2	0% (0)
Decreased appetite	2	0% (0)
Dry eyes	2	0% (0)
Feeling cold	2	0% (0)
Increased seizures	2	50% (1)
Tremors	2	0% (0)
"Wired" feeling	1	0% (0)
Bloating	1	0% (0)
Burping	1	0% (0)
Change in quality of seizures	1	0% (0)
Chest colds	1	0% (0)
Cognitive change	1	0% (0)
Cramping with bowel movement	1	0% (0)
Dysphoria (intense feeling of unease or unpleasantness)	1	0% (0)
Exacerbation of lymphedema	1	10% (1)
Eye muscle twitching	1	0% (0)
Hives	1	0% (0)
Hyperactive bowel sounds	1	0% (0)
Hypomania	1	0% (0)
Increase in mucus secretions	1	100% (1)
Increased aggression	1	100% (1)
Increased urine output	1	0% (0)
Increased yelling	1	0% (0)
Mouth irritation/burning	1	0% (0)
Rash on face	1	0% (0)
Repressed immune system	1	0% (0)
Sleep disturbance	1	0% (0)
Sneezing	1	0% (0)
Thrush	1	0% (0)
Urinary retention	1	0% (0)
Vomiting	1	0% (0)
Worsening acne	1	0% (0)

The 44 severe side effect responses (9.2% of total side effect responses) were attributed to 30 patients (11.0% of patients reporting any side effects). Patients experiencing severe side effects represent a wide range of ages, including children and elderly patients; 14 patients were male and 16 patients were female. Their age, gender, and certifying conditions generally matched the whole first year cohort. Half of patients reporting severe side effects were taking a form of balanced THC:CBD product (n=15); 10 patients were using a high CBD product, 9 patients were using a very high THC product and 4 patients were using a high THC product. Seven of 30 patients (23%) were using a combination of products with varying THC:CBD ratios (the most common combination was very high THC products and 1:1 THC:CBD products); 9 patients used a combination of products with different routes of administration (the most common combination was enteral and inhaled). Refer to Table 7.3 for details on the patients reporting severe side effects, along with the product types that were purchased just prior to experiencing the severe side effect.

PSE-Reported Adverse Side Effects: Conclusions

Less than a quarter of patients from the cohort (~18%) reported adverse side effects within the first 4 months since purchasing their first medical cannabis products. Roughly 90% of those that do report any side effects report 3 or fewer unique side effects during that time period. Results also suggest that relatively few patients experience severe, adverse side effects, with less than 10% of all responses (attributed to 30 patients) being categorized as severe.

Table 7.3. Patients reporting “severe” side effects: patient age, gender, and condition, product types purchased at most recent visit, and type of side effect reported.

Age	Gender	Condition(s)	Very High THC Product(s)	High THC Product(s)	High CBD Product(s)	1:1 THC:CBD Product(s)	Severe Side Effect Reported
55	M	HIV/AIDS	-	-	-	Enteral	Chest pain
67	F	Severe Muscle Spasms	Inhaled	-	Enteral	Enteral, Inhaled	Dry mouth
28	F	Severe Muscle Spasms	-	-	-	Enteral, Inhaled	Lethargy
58	F	Severe Muscle Spasms	-	-	-	Enteral, Inhaled	Panic attack
32	M	Severe Muscle Spasms	Inhaled	-	-	Inhaled	Asthenia (muscle weakness) Lethargy Tachycardia (rapid heart rate)
32	M	Severe Muscle Spasms	Inhaled	-	-	Inhaled	"Stoned" feeling
38	M	Severe Muscle Spasms	Inhaled	-	-	Inhaled	Insomnia
52	F	Severe Muscle Spasms	-	-	-	Enteral, Inhaled	Asthenia (muscle weakness) Drowsiness/somnolence/sedation
61	F	Cancer	-	-	Enteral	Enteral	Dry mouth
36	M	Seizures	-	-	Enteral	-	Diarrhea
41	M	Cancer, Terminal Illness	-	Enteral, Inhaled	-	-	Drowsiness/somnolence/sedation
87	F	Severe Muscle Spasms	-	Enteral, Oromucosal	-	-	Diarrhea
31	M	Cancer	Enteral, Inhaled	-	-	-	Nausea
71	F	Cancer	Inhaled	-	-	Enteral	

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							Asthenia (muscle weakness) Exacerbation of lymphedema
26	F	Terminal Illness	Inhaled	-	-	Enteral, Inhaled, Oromucosal	Constipation Difficulty concentrating Drowsiness/somnolence/sedation Dry mouth Mental clouding/"foggy brain"
36	F	Cancer	-	-	-	Enteral	Headache
33	M	Crohn's Disease	-	-	-	Enteral	Fatigue
63	F	Crohn's Disease	-	-	-	Enteral	Dizziness
82	M	Cancer	-	-	-	Enteral	Dizziness
60	F	Seizures	-	-	Enteral	-	Anxiety
32	M	Seizures	-	-	Enteral	-	Nausea
48	M	Seizures	-	-	Enteral	-	Fatigue
18	F	Seizures	-	-	Enteral	-	Increased seizures
28	M	Seizures	-	-	Enteral	-	Anxiety Paranoia
5	M	Severe Muscle Spasms, Seizures	-	-	Enteral	-	Decreased muscle coordination/balance Increased aggression
10	F	Seizures	-	-	Oromucosal	-	Abdominal/epigastric pain Increase in mucus secretions
56	F	Cancer, HIV/AIDS	-	Enteral	-	-	Dry mouth Euphoria (intense feeling of well- being/pleasure)
21	M	Cancer	-	Inhaled	-	-	Tachycardia (rapid heart rate)
42	F	Severe Muscle Spasms	Inhaled	-	-	-	

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							Impaired memory Difficulty concentration Mental clouding/"foggy brain"
45	F	Severe Muscle Spasms	Inhaled	-	-	-	Numbness

Adverse Side Effects Reported on Surveys

Patient-Reported Negative Effects of Medical Cannabis

For overall patient response rate to the survey three months after first purchase and comparison of responders and non-responders see the section with survey results in the Benefits chapter above.

The Patient Experience survey asks respondents to report the degree, or severity, of any negative effects they believe the patient received from using medical cannabis, on a scale from 1 (no negative effects) to 7 (a great deal of negative effects). The survey then asked the respondent to describe, in their own words, the most significant negative effect. Table 7.4 shows the distribution of negative effects by severity score within three broad categories: physical side effects (including dry mouth, fatigue, headache, dizziness, blurred vision); mental side effects (including mental clouding, paranoia, sedation or symptoms related to “high”); and issues related to accessing the medications (distance to distribution center, inconvenient operating hours for distribution centers, etc.). Based on anticipated reports on the high cost of medication, patients were asked to report on the affordability of the medication separately. However, 53 (7%) patients included cost in their estimation of the most significant negative effects related to medical cannabis; these reports are excluded from Table 7.4 but included in *Appendix E: Patient-Reported Negative Effects from Surveys*. Finally, please see the chapter titled, “Affordability and Suggestions for Improvement” for patient perceptions of medication affordability.

Of 792 completed patient surveys, 744 responses (94%) included a negative effects score and 441 (56%) included a response regarding most important negative effect, including comments stating “no negative effect.” Of 744 negative effect scale responses, 452 (61%) reported a score of 1, or “no negative effect.” This includes 13 patients who, though they entered a score of 1, entered a narrative description of physical or mental side effects. A total of 195 responses (25% of all patient responses) reported physical or mental negative effects. These reports generally mirrored side effects reported in clinical trials of medical cannabis (see “[A Review of Medical Cannabis Studies relating to Chemical Compositions and Dosages for Qualifying Medical Conditions](#)” on the [Office of Medical Cannabis](#) website). Reports of the most severe negative effects were as follows: scores of 7 (great deal of negative effects) were associated with reports of allergic reaction (n=1), pain (n=1), severe diarrhea (n=1), change in mood/behavior (n=1) and decreased awareness of surroundings (n=1). Scores of 6 were associated with reported physical side effects of dizziness or related symptoms (n=3), severe diarrhea (n=1), stomach pain (n=1), burning sensation with sublingual product (n=1), sleeping problems (n=1) and worsening seizures (n=2), and mental side effects of crying and irritability (n=1). Scores of 5 which reported physical negative effects included drug interactions, increased seizure activity, allergic reaction, lightheadedness, fatigue, headaches, visual impairment, dry mouth, a report that the

product “made me sick” and pain related to vaping (n=1 each). Scores of 5 which reported mental negative effects included reports of paranoia (n=2), inability to concentrate (n=1), and increased anxiety (n=1).

Apart from physical or mental negative effects, some patients reported issues related to program access, including distance to the nearest cannabis patient center (n=13). Other negative effects (not included in Table 7.4) were reported including issues related to the program design (n=9), negative attitudes of others toward the patient’s use of medical cannabis (n=17) and fear of legal or employment-related consequences related to program participation (n=5). Finally, 16 reports of negative effects were related to lack of efficacy of the medicine in treating the patient’s condition. A full listing of patient-reported negative effect comments is available in *Appendix E: Patient-Reported Negative Effects from Surveys*.

Table 7.4. Summary of most significant negative effects experienced by the patient, per patient reports.

	1: No Negative Effects	2	3	4	5	6	7: Great Deal of Negative Effects	Total
Physical Side Effects	10 (1%)	57 (7%)	15 (2%)	26 (3%)	10 (1%)	9 (1%)	3 (0%)	130 (16%)
Mental Side Effects	3 (0%)	18 (2%)	14 (2%)	19 (2%)	4 (1%)	1 (0%)	2 (0%)	61 (8%)
Access-Related Issues	4 (1%)	3 (1%)	1 (0%)	2 (0%)	1 (0%)	1 (0%)	1 (0%)	13 (2%)

Note: Results are broken down by negative effect scale scores. Percentages are calculated based on the total number of patient survey responses received (n=792).

HCP-Reported Negative Effects from Medical Cannabis

Like the Patient Experience survey, the HCP survey asks respondents to report the degree, or severity, of any negative effects they believe the patient received from using medical cannabis, on a scale from 1 (no negative effects) to 7 (a great deal of negative effects). Table 7.5 shows the distribution of negative effects by severity score within three broad categories: physical side effects (including dry mouth, fatigue, headache, dizziness, blurred vision); mental side effects (including mental clouding, paranoia, sedation or symptoms related to “high”); and issues related to accessing the medications (long distance to distribution center, inconvenient operating hours for distribution centers, etc.).

Of 251 total HCP survey responses, 200 responses (80%) included a negative effects score and 107 responses (43%) included a description of any negative effect(s). Of 200 negative effect scale responses, 128 (64%) reported a score of 1, or “no negative effect.” This includes 6 HCP

reports which entered a narrative description of physical or mental side effects. There were 33 HCP reports (13% of all HCP survey responses) of physical or mental negative effects resulting from medical cannabis treatment. As seen in the patient survey results, these generally mirrored side effects described in clinical trials (see [“A Review of Medical Cannabis Studies relating to Chemical Compositions and Dosages for Qualifying Medical Conditions”](#) on the [Office of Medical Cannabis](#) website). Healthcare providers describing negative effects with high scores reported the following: a score of 7 was associated with a report of “abdominal discomfort”; dizziness (n=1) and sedation (n=1) were reported with scores of 6; finally, constipation, lethargy and worsened seizure activity (n=1) and a report of “too strong per patient” (n=1) were associated with a score of 5. Four HCP responses reported access-related issues as a negative effect. Additionally, 25 HCP reports (10% of all HCP survey responses) described cost as a negative effect related to medical cannabis (these reports are not included in Table 7.5).

A full listing of all negative effect comments from HCPs can be found in *Appendix F: Healthcare Practitioner-Reported Negative Effects from Surveys*.

Table 7.5. Summary of most significant negative effects experienced by the patient, per HCP reports.

Negative Effects By Score (1-7 Scale)	1 (No Negative Effects)	2	3	4	5	6	7 (Great Deal of Negative Effects)	Total
<i>Physical Side Effects</i>	4 (2%)	5 (2%)	6 (2%)	2 (1%)	1 (0%)	1 (0%)	1 (0%)	20 (8%)
<i>Mental Side Effects</i>	2 (1%)	6 (2%)	3 (1%)	1 (0%)	-	1 (0%)	-	13 (5%)
<i>Access Issues</i>	1 (0%)	2 (1%)	1 (0%)	-	-	-	-	4 (2%)

Note: Results are broken down by negative effect scale scores. Percentages in each cell are based on the total number of HCP survey responses (n=251).

Adverse Side Effects Reported on Surveys: Conclusions

Based on data from surveys completed by patients and their certifying healthcare practitioners three months after the patient’s first medical cannabis purchase, 25% of patient respondents report physical or mental side effects related to medical cannabis use. A minority of healthcare provider responders (13%) report physical or mental side effects. Both groups describe negative effects related to medical cannabis use including the cost of products and issues related to

accessing medicine. Most patients and HCPs reporting physical or mental side effects report low degrees of severity (negative effect scale scores of 1-3).

Adverse Event Reporting to Manufacturers

There is potential for enrolled patients, their family and caregivers, and health care practitioners to be concerned about an adverse event potentially caused by medical cannabis and to want to register their concern quickly. Both manufacturers have processes in place to receive these messages by telephone and by email. They collect and document information related to the incident and report it to the Office of Medical Cannabis. In nature and severity these reports have been similar to the adverse events reported in Patient Self-Evaluations and surveys.

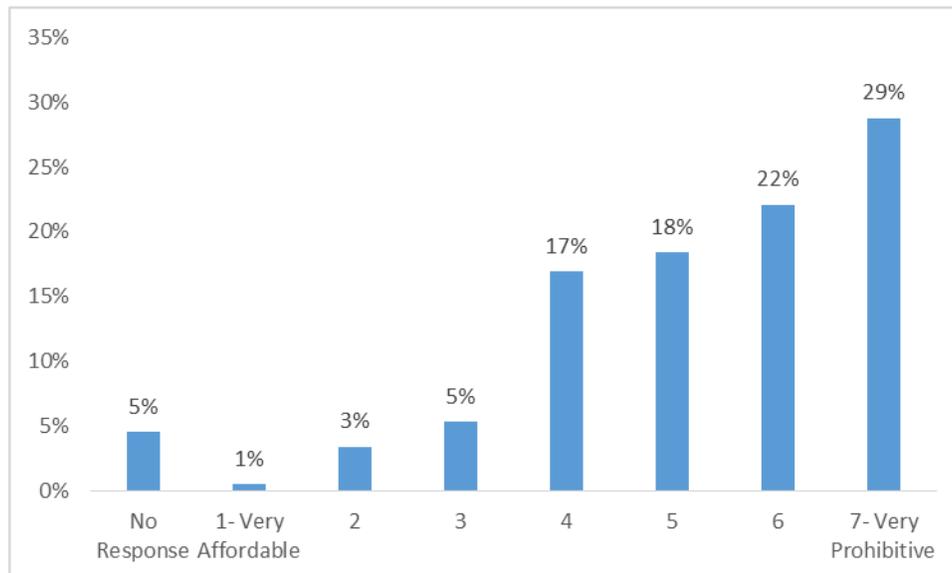
Patients, their registered caregivers, and certifying health care practitioners have a duty as program participants to report serious adverse events. Called “serious adverse incidents” in the program’s rules (4770.4002), these are essentially occurrences that lead to hospitalization or are life-threatening events. As of the date of this report, no reported adverse events have met the definition of “serious adverse incident.”

8. Affordability and Suggestions for Improving the Program

Patient Perceptions of Affordability

Unlike traditional pharmaceuticals whose costs are often covered through insurance reimbursement, medical cannabis must be purchased solely out of pocket. The Patient Experience survey asked patients to rate the cost of the medication on a scale from 1, or very affordable, to 7, or very prohibitive. Responses to this question are displayed in Figure 8.1. Of 792 respondents, 683 (86%) reported that they found medical cannabis to be at least somewhat unaffordable (score of 4 or greater).

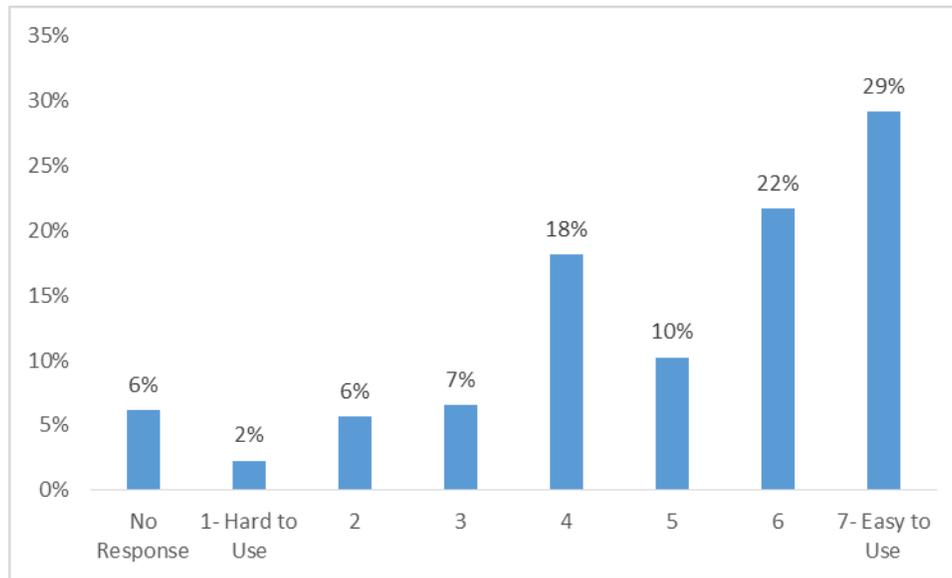
Figure 8.1. Patient Perceptions of Product Affordability



Patient Perceptions of Online Registry

Patients were asked how easy or difficult the online registry system, through which the Minnesota Medical Cannabis program is administered, is to use. Patients were asked to rate usability on a scale from 1, or very difficult to use, to 7, or very easy or intuitive to use. Responses were generally positive (Figure 2), with 51% of patients reporting high scores of usability (6 or 7).

Figure 8.2. Online Registry Ease of Use

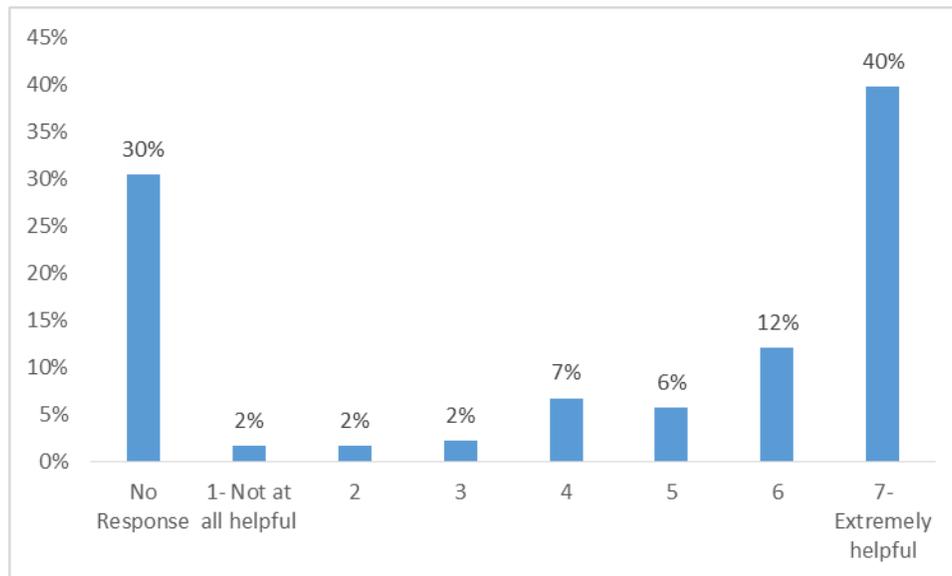


Patient reports on the ease of use of the Medical Cannabis Registry online system (1=very difficult to use; 4=neither difficult nor easy to use; 7=very easy/intuitive to use). Note: percentages are based on total number of patient responses; 49 patients did not complete this question and are not represented in the figure.

Patient Perceptions of Office of Medical Cannabis Call Center

Patients were asked to rate the helpfulness of the Office of Medical Cannabis Call Center (also known at the Support Center), which provides support for patients, caregivers and providers in navigating the registration and enrollment process as well as assisting with other program-related inquiries. The Patient Experience survey asked patients to rate the helpfulness of the call center on a scale from 1, or not very helpful, to 7, or very helpful. Over half of all patient responses reported high scores of helpfulness (6 or 7).

Figure 8.3. Call Center Helpfulness

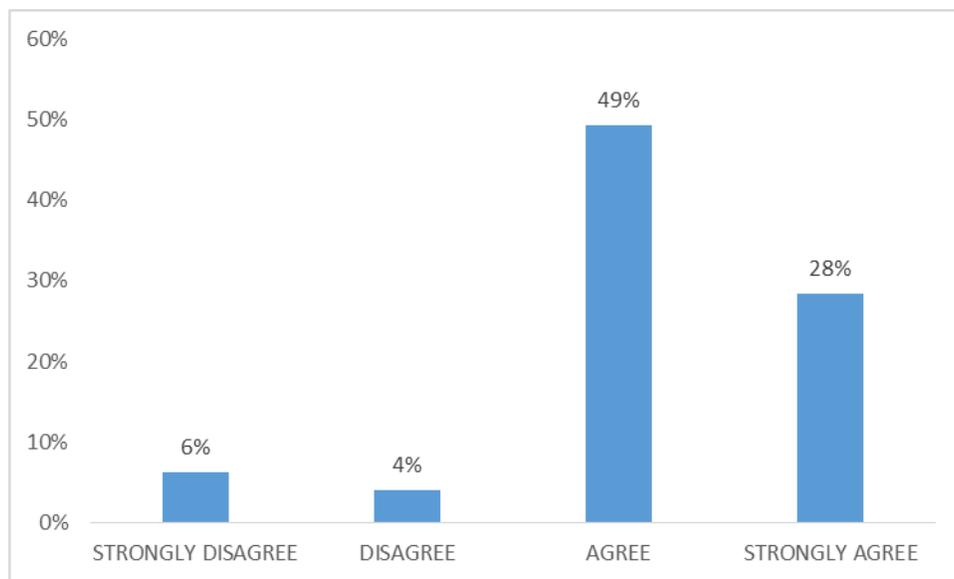


Patient reports on the helpfulness of the Office of Medical Cannabis Patient Support Center (1=not very helpful; 4=somewhat helpful; 7=very helpful). Note: percentages are based on total number of patient responses; 241 patients did not complete this question (several indicated no experience with the call center) and are not represented in the figure.

Patient Perceptions of Office of Medical Cannabis Website

Patients were asked to state their level of agreement with the statement: “The Office of Medical Cannabis website provides me with the information I need to understand and participate in the program.” Among all patient respondents, 49% agreed and 28% strongly agreed that the website met their needs for information; however 10% expressed that they did not feel the website met their needs for program participation (Figure 8.4) and 12% did not respond to the survey question.

Figure 8.4. “The website provides the information I need to understand and participate in the program”



Patient Suggestions

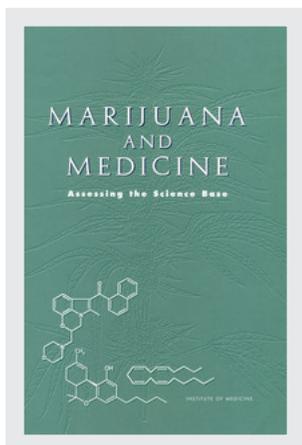
Patients were asked to provide feedback on the program; all responses submitted from the first year cohort are tabulated in *Appendix G: Patient Suggestions for Improving the Program from Surveys*. Many patients used this space to elaborate on the program’s impact on their lives; others suggested changes to the program’s administration or reported concerns related to product cost or access to cannabis patient centers.

Suggestions and Information Requests from Healthcare Practitioners

Healthcare practitioners were asked to provide suggestions for improving the program, and were also asked if any additional information from the program would be useful to them. The full tabulation of comments is available in *Appendix H: Healthcare Practitioner Suggestions for Improving the Program and Requests for Additional Information from Surveys*. Many comments reported in these sections of the survey mirrored those reported as clinical observations; there were 39 additional comments relating to affordability of the products. Other common responses included requests for information on medical cannabis dosing and specific information on what products their patient was purchasing. Other responses included requests for more patient education regarding products, information on drug interactions, and data on efficacy in specific patient populations.

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CONTRIBUTORS

Janet E. Joy, Stanley J. Watson, Jr., and John A. Benson, Jr., Editors;
Institute of Medicine

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MARIJUANA
AND MEDICINE
Assessing the Science Base

Janet E. Joy, Stanley J. Watson, Jr., and
John A. Benson, Jr., *Editors*

Division of Neuroscience and Behavioral Health

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logo-type by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

PRINCIPAL INVESTIGATORS AND ADVISORY PANEL

JOHN A. BENSON, JR. (*Co-Principal Investigator*), Dean and Professor of Medicine, Emeritus, Oregon Health Sciences University School of Medicine

STANLEY J. WATSON, JR. (*Co-Principal Investigator*), Co-Director and Research Scientist, Mental Health Research Institute, University of Michigan

STEVEN R. CHILDERS, Professor of Physiology and Pharmacology, Center for Neuroscience, Bowman Gray School of Medicine, Wake Forest University

J. RICHARD CROUT, President of Crout Consulting, Drug Development and Regulation, Bethesda, Maryland

THOMAS J. CROWLEY, Professor, Department of Psychiatry, and Executive Director, Addiction Research and Treatment Services, University of Colorado Health Sciences Center

JUDITH FEINBERG, Professor, Department of Internal Medicine, and Associate Director, Division of Infectious Diseases, University of Cincinnati School of Medicine

HOWARD L. FIELDS, Professor of Neurology and Physiology, University of California at San Francisco

DOROTHY HATSUKAMI, Professor of Psychiatry, University of Minnesota

ERIC B. LARSON, Medical Director, University of Washington Medical Center, and Associate Dean for Clinical Affairs, University of Washington

BILLY R. MARTIN, Professor of Pharmacology and Toxicology, and Director of National Institute on Drug Abuse Center on Drug Abuse, Medical College of Virginia, Virginia Commonwealth University

TIMOTHY L. VOLLMER, Professor of Medicine, Multiple Sclerosis Research Center, Yale University School of Medicine

Study Staff

JANET E. JOY, Study Director

DEBORAH O. YARNELL, Research Associate

AMELIA B. MATHIS, Project Assistant

CHERYL MITCHELL, Administrative Assistant (until September 1998)

THOMAS J. WETTERHAN, Research Assistant (until September 1998)

CONSTANCE M. PECHURA, Division Director (until April 1998)

NORMAN GROSSBLATT, Manuscript Editor

Consultant

MIRIAM DAVIS

Section Staff

CHARLES H. EVANS, JR., Head, Health Sciences Section

LINDA DEPUGH, Administrative Assistant

CARLOS GABRIEL, Financial Associate

Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the Institute of Medicine in making the published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. The committee wishes to thank the following individuals for their participation in the review of this report:

JAMES C. ANTHONY, Johns Hopkins University
JACK D. BARCHAS, Cornell University Medical College
SUMNER H. BURSTEIN, University of Massachusetts Medical School
AVRAM GOLDSTEIN, Stanford University
LESTER GRINSPOON, Harvard Medical School
MILES HERKENHAM, National Institute of Mental Health, National
Institutes of Health, Bethesda, Maryland
HERBERT D. KLEBER, Columbia University
GEOFFREY M. LEVITT, Venable Attorneys at Law, Washington, D.C.
KENNETH P. MACKIE, University of Washington
RAPHAEL MECHOULAM, The Hebrew University of Jerusalem
CHARLES P. O'BRIEN, University of Pennsylvania
JUDITH G. RABKIN, Columbia University

ERIC G. VOTH, International Drug Strategy Institute, Topeka, Kansas
VIRGINIA V. WELDON, Washington University

While the individuals listed above provided constructive comments and suggestions, it must be emphasized that responsibility for the final content of this report rests entirely with the authoring committee and the Institute of Medicine.

Preface



Public opinion on the medical value of marijuana has been sharply divided. Some dismiss medical marijuana as a hoax that exploits our natural compassion for the sick; others claim it is a uniquely soothing medicine that has been withheld from patients through regulations based on false claims. Proponents of both views cite “scientific evidence” to support their views and have expressed those views at the ballot box in recent state elections. In January 1997, the White House Office of National Drug Control Policy (ONDCP) asked the Institute of Medicine to conduct a review of the scientific evidence to assess the potential health benefits and risks of marijuana and its constituent cannabinoids. That review began in August 1997 and culminates with this report.

The ONDCP request came in the wake of state “medical marijuana” initiatives. In November 1996, voters in California and Arizona passed referenda designed to permit the use of marijuana as medicine. Although Arizona’s referendum was invalidated five months later, the referenda galvanized a national response. In November 1998, voters in six states (Alaska, Arizona, Colorado, Nevada, Oregon, and Washington) passed ballot initiatives in support of medical marijuana. (The Colorado vote will not count, however, because after the vote was taken a court ruling determined there had not been enough valid signatures to place the initiative on the ballot.)

Information for this study was gathered through scientific workshops, site visits to cannabis buyers' clubs and HIV/AIDS clinics, analysis of the relevant scientific literature, and extensive consultation with biomedical and social scientists. The three 2-day workshops—in Irvine, California; New Orleans, Louisiana; and Washington, D.C.—were open to the public and included scientific presentations and individual reports, mostly from patients and their families, about experiences with and perspectives on the medical use of marijuana. Scientific experts in various fields were selected to talk about the latest research on marijuana, cannabinoids, and related topics. (Cannabinoids are drugs with actions similar to THC, the primary psychoactive ingredient in marijuana.) In addition, advocates for and against the medical use of marijuana were invited to present scientific evidence in support of their positions. Finally, the Institute of Medicine appointed a panel of nine experts to advise the study team on technical issues.

Public outreach included setting up a Web site that provided information about the study and asked for input from the public. The Web site was open for comment from November 1997 until November 1998. Some 130 organizations were invited to participate in the public workshops. Many people in the organizations—particularly those opposed to the medical use of marijuana—felt that a public forum was not conducive to expressing their views; they were invited to communicate their opinions (and reasons for holding them) by mail or telephone. As a result, roughly equal numbers of persons and organizations opposed to and in favor of the medical use of marijuana were heard from.

Advances in cannabinoid science over the past 16 years have given rise to a wealth of new opportunities for the development of medically useful cannabinoid-based drugs. The accumulated data suggest a variety of indications, particularly for pain relief, antiemesis, and appetite stimulation. For patients who suffer simultaneously from severe pain, nausea, and appetite loss, such as those with AIDS or who are undergoing chemotherapy, cannabinoid drugs might offer broad-spectrum relief not found in any other single medication.

Marijuana is not a completely benign substance. It is a powerful drug with a variety of effects. However, the harmful effects to individuals from the perspective of possible medical use of marijuana are not necessarily the same as the harmful physical effects of drug abuse.

Although marijuana smoke delivers THC and other cannabinoids to the body, it also delivers harmful substances, including most of those found in tobacco smoke. In addition, plants contain a variable mixture of biologically active compounds and cannot be expected to provide a pre-

cisely defined drug effect. For those reasons, the report concludes that the future of cannabinoid drugs lies not in smoked marijuana but in chemically defined drugs that act on the cannabinoid systems that are a natural component of human physiology. Until such drugs can be developed and made available for medical use, the report recommends interim solutions.

John A. Benson, Jr.
Stanley J. Watson, Jr.
Co-Principal Investigators

Acknowledgments



This report covers such a broad range of disciplines—neuroscience, pharmacology, immunology, drug abuse, drug laws, and a variety of medical specialties, including neurology, oncology, infectious diseases, and ophthalmology—that it would not have been complete without the generous support of many people. Our goal in preparing this report was to identify the solid ground of scientific consensus and to steer clear of the muddy distractions of opinions that are inconsistent with careful scientific analysis. To this end we consulted extensively with experts in each of the disciplines covered in this report. We are deeply indebted to each of them.

Members of the Advisory Panel, selected because each is recognized as among the most accomplished in their respective disciplines (see page iii), provided guidance to the study team throughout the study—from helping to lay the intellectual framework to reviewing early drafts of the report.

The following people wrote invaluable background papers for the report: Steven R. Childers, Paul Consroe, Howard Fields, Richard J. Gralla, Norbert Kaminski, Paul Kaufman, Thomas Klein, Donald Kotler, Richard Musty, Clara Sanudo-Peña, C. Robert Schuster, Stephen Sidney, Donald P. Tashkin, and J. Michael Walker. Others provided expert technical commentary on draft sections of the report: Richard Bonnie, Keith Green, Frederick Fraunfelder, Andrea Hohmann, John McAnulty, Craig Nichols, John Nutt, and Robert Pandina. Still others responded to many inquiries, provided expert counsel, or shared their unpublished data: Paul Consroe, Geoffrey Levitt, Raphael Mechoulam, Richard Musty, David Pate, Roger

Pertwee, Clara Sanudo-Peña, Carl Soderstrom, J. Michael Walker, and Scott Yarnell. Miriam Davis, consultant to the study team, provided excellent written material for the chapter on cannabinoid drug development.

The reviewers for the report (see page iv) provided extensive, constructive suggestions for improving the report. It was greatly enhanced by their thoughtful attention. Many of these people assisted us through many iterations of the report. All of them made contributions that were essential to the strength of the report. At the same time, it must be emphasized that responsibility for the final content of report rests entirely with the authors and the Institute of Medicine.

We would also like to thank the people who hosted our visits to their organizations. They were unfailingly helpful and generous with their time. Jeffrey Jones and members of the Oakland Cannabis Buyers' Cooperative, Denis Peron of the San Francisco Cannabis Cultivators Club, Scott Imler and staff at the Los Angeles Cannabis Resource Center, Victor Hernandez and members of Californians Helping Alleviate Medical Problems (CHAMPS), Michael Weinstein of the AIDS Health Care Foundation, and Marsha Bennett of the Louisiana State University Medical Center. We also appreciate the many people who spoke at the public workshops or wrote to share their views on the medical use of marijuana (see Appendix A).

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Deborah Yarnell's contribution as research associate for this study was outstanding. She organized site visits, researched and drafted technical material for the report, and consulted extensively with relevant experts to ensure the technical accuracy of the text. The quality of her contributions throughout this study was exemplary.

Finally, the principal investigators on this study wish to personally thank Janet Joy for her deep commitment to the science and shape of this report. In addition, her help in integrating the entire data gathering and information organization of this report was nothing short of essential. Her knowledge of neurobiology, her sense of quality control, and her unflinching spirit over the 18 months illuminated the subjects and were indispensable to the study's successful completion.

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MARIJUANA AND MEDICINE

Executive Summary



Public opinion on the medical value of marijuana has been sharply divided. Some dismiss medical marijuana as a hoax that exploits our natural compassion for the sick; others claim it is a uniquely soothing medicine that has been withheld from patients through regulations based on false claims. Proponents of both views cite “scientific evidence” to support their views and have expressed those views at the ballot box in recent state elections. In January 1997, the White House Office of National Drug Control Policy (ONDCP) asked the Institute of Medicine (IOM) to conduct a review of the scientific evidence to assess the potential health benefits and risks of marijuana and its constituent cannabinoids (see the Statement of Task on page 9). That review began in August 1997 and culminates with this report.

The ONDCP request came in the wake of state “medical marijuana” initiatives. In November 1996, voters in California and Arizona passed referenda designed to permit the use of marijuana as medicine. Although Arizona’s referendum was invalidated five months later, the referenda galvanized a national response. In November 1998, voters in six states (Alaska, Arizona, Colorado, Nevada, Oregon, and Washington) passed ballot initiatives in support of medical marijuana. (The Colorado vote will not count, however, because after the vote was taken a court ruling determined there had not been enough valid signatures to place the initiative on the ballot.)

Can marijuana relieve health problems? Is it safe for medical use?

Those straightforward questions are embedded in a web of social concerns, most of which lie outside the scope of this report. Controversies concerning the nonmedical use of marijuana spill over into the medical marijuana debate and obscure the real state of scientific knowledge. In contrast with the many disagreements bearing on social issues, the study team found substantial consensus among experts in the relevant disciplines on the scientific evidence about potential medical uses of marijuana.

This report summarizes and analyzes what is known about the medical use of marijuana; it emphasizes evidence-based medicine (derived from knowledge and experience informed by rigorous scientific analysis), as opposed to belief-based medicine (derived from judgment, intuition, and beliefs untested by rigorous science).

Throughout this report, *marijuana* refers to unpurified plant substances, including leaves or flower tops whether consumed by ingestion or smoking. References to the “effects of marijuana” should be understood to include the composite effects of its various components; that is, the effects of tetrahydrocannabinol (THC), which is the primary psychoactive ingredient in marijuana, are included among its effects, but not all the effects of marijuana are necessarily due to THC. *Cannabinoids* are the group of compounds related to THC, whether found in the marijuana plant, in animals, or synthesized in chemistry laboratories.

Three focal concerns in evaluating the medical use of marijuana are:

1. Evaluation of the effects of isolated cannabinoids;
2. Evaluation of the risks associated with the medical use of marijuana; and
3. Evaluation of the use of smoked marijuana.

EFFECTS OF ISOLATED CANNABINOIDS

Cannabinoid Biology

Much has been learned since the 1982 IOM report *Marijuana and Health*. Although it was clear then that most of the effects of marijuana were due to its actions on the brain, there was little information about how THC acted on brain cells (neurons), which cells were affected by THC, or even what general areas of the brain were most affected by THC. In addition, too little was known about cannabinoid physiology to offer any scientific insights into the harmful or therapeutic effects of marijuana. That all changed with the identification and characterization of cannabinoid receptors in the 1980s and 1990s. During the past 16 years, science has advanced greatly and can tell us much more about the potential medical benefits of cannabinoids.

CONCLUSION: At this point, our knowledge about the biology of marijuana and cannabinoids allows us to make some general conclusions:

- Cannabinoids likely have a natural role in pain modulation, control of movement, and memory.
- The natural role of cannabinoids in immune systems is likely multi-faceted and remains unclear.
- The brain develops tolerance to cannabinoids.
- Animal research demonstrates the potential for dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine, or nicotine.
- Withdrawal symptoms can be observed in animals but appear to be mild compared to opiates or benzodiazepines, such as diazepam (Valium).

CONCLUSION: The different cannabinoid receptor types found in the body appear to play different roles in normal human physiology. In addition, some effects of cannabinoids appear to be independent of those receptors. The variety of mechanisms through which cannabinoids can influence human physiology underlies the variety of potential therapeutic uses for drugs that might act selectively on different cannabinoid systems.

RECOMMENDATION 1: Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoid research should include, but not be restricted to, effects attributable to THC alone.

Efficacy of Cannabinoid Drugs

The accumulated data indicate a potential therapeutic value for cannabinoid drugs, particularly for symptoms such as pain relief, control of nausea and vomiting, and appetite stimulation. The therapeutic effects of cannabinoids are best established for THC, which is generally one of the two most abundant of the cannabinoids in marijuana. (Cannabidiol is generally the other most abundant cannabinoid.)

The effects of cannabinoids on the symptoms studied are generally modest, and in most cases there are more effective medications. However, people vary in their responses to medications, and there will likely always be a subpopulation of patients who do not respond well to other

medications. The combination of cannabinoid drug effects (anxiety reduction, appetite stimulation, nausea reduction, and pain relief) suggests that cannabinoids would be moderately well suited for particular conditions, such as chemotherapy-induced nausea and vomiting and AIDS wasting.

Defined substances, such as purified cannabinoid compounds, are preferable to plant products, which are of variable and uncertain composition. Use of defined cannabinoids permits a more precise evaluation of their effects, whether in combination or alone. Medications that can maximize the desired effects of cannabinoids and minimize the undesired effects can very likely be identified.

Although most scientists who study cannabinoids agree that the pathways to cannabinoid drug development are clearly marked, there is no guarantee that the fruits of scientific research will be made available to the public for medical use. Cannabinoid-based drugs will only become available if public investment in cannabinoid drug research is sustained and if there is enough incentive for private enterprise to develop and market such drugs.

CONCLUSION: Scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily THC, for pain relief, control of nausea and vomiting, and appetite stimulation; smoked marijuana, however, is a crude THC delivery system that also delivers harmful substances.

RECOMMENDATION 2: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.

Influence of Psychological Effects on Therapeutic Effects

The psychological effects of THC and similar cannabinoids pose three issues for the therapeutic use of cannabinoid drugs. First, for some patients—particularly older patients with no previous marijuana experience—the psychological effects are disturbing. Those patients report experiencing unpleasant feelings and disorientation after being treated with THC, generally more severe for oral THC than for smoked marijuana. Second, for conditions such as movement disorders or nausea, in which anxiety exacerbates the symptoms, the antianxiety effects of cannabinoid drugs can influence symptoms indirectly. This can be beneficial or can create false impressions of the drug effect. Third, for cases in which symptoms are multifaceted, the combination of THC effects might provide a form of adjunctive therapy; for example, AIDS wasting patients would likely benefit from a medication that simultaneously reduces anxiety, pain, and nausea while stimulating appetite.

CONCLUSION: The psychological effects of cannabinoids, such as anxiety reduction, sedation, and euphoria can influence their potential therapeutic value. Those effects are potentially undesirable for certain patients and situations and beneficial for others. In addition, psychological effects can complicate the interpretation of other aspects of the drug's effect.

RECOMMENDATION 3: Psychological effects of cannabinoids such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.

RISKS ASSOCIATED WITH MEDICAL USE OF MARIJUANA

Physiological Risks

Marijuana is not a completely benign substance. It is a powerful drug with a variety of effects. However, except for the harms associated with smoking, the adverse effects of marijuana use are within the range of effects tolerated for other medications. The harmful effects to individuals from the perspective of possible medical use of marijuana are not necessarily the same as the harmful physical effects of drug abuse. When interpreting studies purporting to show the harmful effects of marijuana, it is important to keep in mind that the majority of those studies are based on *smoked* marijuana, and cannabinoid effects cannot be separated from the effects of inhaling smoke from burning plant material and contaminants.

For most people the primary adverse effect of *acute* marijuana use is diminished psychomotor performance. It is, therefore, inadvisable to operate any vehicle or potentially dangerous equipment while under the influence of marijuana, THC, or any cannabinoid drug with comparable effects. In addition, a minority of marijuana users experience dysphoria, or unpleasant feelings. Finally, the short-term immunosuppressive effects are not well established but, if they exist, are not likely great enough to preclude a legitimate medical use.

The *chronic* effects of marijuana are of greater concern for medical use and fall into two categories: the effects of chronic smoking and the effects of THC. Marijuana smoking is associated with abnormalities of cells lining the human respiratory tract. Marijuana smoke, like tobacco smoke, is associated with increased risk of cancer, lung damage, and poor pregnancy outcomes. Although cellular, genetic, and human studies all suggest that marijuana smoke is an important risk factor for the development of respiratory cancer, proof that habitual marijuana smoking does or does not cause cancer awaits the results of well-designed studies.

CONCLUSION: Numerous studies suggest that marijuana smoke is an important risk factor in the development of respiratory disease.

RECOMMENDATION 4: Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent.

Marijuana Dependence and Withdrawal

A second concern associated with chronic marijuana use is dependence on the psychoactive effects of THC. Although few marijuana users develop dependence, some do. Risk factors for marijuana dependence are similar to those for other forms of substance abuse. In particular, anti-social personality and conduct disorders are closely associated with substance abuse.

CONCLUSION: A distinctive marijuana withdrawal syndrome has been identified, but it is mild and short lived. The syndrome includes restlessness, irritability, mild agitation, insomnia, sleep disturbance, nausea, and cramping.

Marijuana as a “Gateway” Drug

Patterns in progression of drug use from adolescence to adulthood are strikingly regular. Because it is the most widely used illicit drug, marijuana is predictably the first illicit drug most people encounter. Not surprisingly, most users of other illicit drugs have used marijuana first. In fact, most drug users begin with alcohol and nicotine before marijuana—usually before they are of legal age.

In the sense that marijuana use typically precedes rather than follows initiation of other illicit drug use, it is indeed a “gateway” drug. But because underage smoking and alcohol use typically precede marijuana use, marijuana is not the most common, and is rarely the first, “gateway” to illicit drug use. There is no conclusive evidence that the drug effects of marijuana are causally linked to the subsequent abuse of other illicit drugs. An important caution is that data on drug use progression cannot be assumed to apply to the use of drugs for medical purposes. It does not follow from those data that if marijuana were available by prescription for medical use, the pattern of drug use would remain the same as seen in illicit use.

Finally, there is a broad social concern that sanctioning the medical use of marijuana might increase its use among the general population. At

this point there are no convincing data to support this concern. The existing data are consistent with the idea that this would not be a problem if the medical use of marijuana were as closely regulated as other medications with abuse potential.

CONCLUSION: Present data on drug use progression neither support nor refute the suggestion that medical availability would increase drug abuse. However, this question is beyond the issues normally considered for medical uses of drugs and should not be a factor in evaluating the therapeutic potential of marijuana or cannabinoids.

USE OF SMOKED MARIJUANA

Because of the health risks associated with smoking, smoked marijuana should generally not be recommended for long-term medical use. Nonetheless, for certain patients, such as the terminally ill or those with debilitating symptoms, the long-term risks are not of great concern. Further, despite the legal, social, and health problems associated with smoking marijuana, it is widely used by certain patient groups.

RECOMMENDATION 5: Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than six months), should be conducted in patients with conditions for which there is reasonable expectation of efficacy, should be approved by institutional review boards, and should collect data about efficacy.

The goal of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug but rather to serve as a first step toward the possible development of nonsmoked rapid-onset cannabinoid delivery systems. However, it will likely be many years before a safe and effective cannabinoid delivery system, such as an inhaler, is available for patients. In the meantime there are patients with debilitating symptoms for whom smoked marijuana might provide relief. The use of smoked marijuana for those patients should weigh both the expected efficacy of marijuana and ethical issues in patient care, including providing information about the known and suspected risks of smoked marijuana use.

RECOMMENDATION 6: Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:

- **failure of all approved medications to provide relief has been documented,**
- **the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs,**
- **such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness, and**
- **involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.**

Until a nonsmoked rapid-onset cannabinoid drug delivery system becomes available, we acknowledge that there is no clear alternative for people suffering from *chronic* conditions that might be relieved by smoking marijuana, such as pain or AIDS wasting. One possible approach is to treat patients as *n-of-1* clinical trials (single-patient trials), in which patients are fully informed of their status as experimental subjects using a harmful drug delivery system and in which their condition is closely monitored and documented under medical supervision, thereby increasing the knowledge base of the risks and benefits of marijuana use under such conditions.

STATEMENT OF TASK

The study will assess what is currently known and not known about the medical use of marijuana. It will include a review of the science base regarding the mechanism of action of marijuana, an examination of the peer-reviewed scientific literature on the efficacy of therapeutic uses of marijuana, and the costs of using various forms of marijuana versus approved drugs for specific medical conditions (e.g., glaucoma, multiple sclerosis, wasting diseases, nausea, and pain).

The study will also include an evaluation of the acute and chronic effects of marijuana on health and behavior; a consideration of the adverse effects of marijuana use compared with approved drugs; an evaluation of the efficacy of different delivery systems for marijuana (e.g., inhalation vs. oral); an analysis of the data concerning marijuana as a gateway drug; and an examination of the possible differences in the effects of marijuana due to age and type of medical condition.

Specific Issues

Specific issues to be addressed fall under three broad categories: science base, therapeutic use, and economics.

Science Base

- Review of the neuroscience related to marijuana, particularly the relevance of new studies on addiction and craving
- Review of the behavioral and social science base of marijuana use, particularly an assessment of the relative risk of progression to other drugs following marijuana use
- Review of the literature determining which chemical components of crude marijuana are responsible for possible therapeutic effects and for side effects

Therapeutic Use

- Evaluation of any conclusions on the medical use of marijuana drawn by other groups
- Efficacy and side effects of various delivery systems for marijuana compared to existing medications for glaucoma, wasting syndrome, pain, nausea, or other symptoms
- Differential effects of various forms of marijuana that relate to age or type of disease

Economics

- Costs of various forms of marijuana compared with costs of existing medications for glaucoma, wasting syndrome, pain, nausea, or other symptoms
- Assessment of differences between marijuana and existing medications in terms of access and availability

RECOMMENDATIONS

RECOMMENDATION 1: Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoid research should include, but not be restricted to, effects attributable to THC alone.

Scientific data indicate the potential therapeutic value of cannabinoid drugs for pain relief, control of nausea and vomiting, and appetite stimulation. This value would be enhanced by a rapid onset of drug effect.

RECOMMENDATION 2: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.

The psychological effects of cannabinoids are probably important determinants of their potential therapeutic value. They can influence symptoms indirectly which could create false impressions of the drug effect or be beneficial as a form of adjunctive therapy.

RECOMMENDATION 3: Psychological effects of cannabinoids such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.

Numerous studies suggest that marijuana smoke is an important risk factor in the development of respiratory diseases, but the data that could conclusively establish or refute this suspected link have not been collected.

RECOMMENDATION 4: Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent.

Because marijuana is a crude THC delivery system that also delivers harmful substances, smoked marijuana should generally not be recom-

mended for medical use. Nonetheless, marijuana is widely used by certain patient groups, which raises both safety and efficacy issues.

RECOMMENDATION 5: Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than six months), should be conducted in patients with conditions for which there is reasonable expectation of efficacy, should be approved by institutional review boards, and should collect data about efficacy.

If there is any future for marijuana as a medicine, it lies in its isolated components, the cannabinoids and their synthetic derivatives. Isolated cannabinoids will provide more reliable effects than crude plant mixtures. Therefore, the purpose of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug but rather to serve as a first step toward the development of nonsmoked rapid-onset cannabinoid delivery systems.

RECOMMENDATION 6: Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:

- **failure of all approved medications to provide relief has been documented,**
- **the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs,**
- **such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness, and**
- **involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.**

1

Introduction



This report summarizes and analyzes what is known about the medical use of marijuana; it emphasizes evidence-based medicine (derived from knowledge and experience informed by rigorous scientific analysis), as opposed to belief-based medicine (derived from judgment, intuition, and beliefs untested by rigorous science).

Scientific data on controversial subjects are commonly misinterpreted, overinterpreted, and misrepresented, and the medical marijuana debate is no exception. We have tried to present the scientific studies in such a way as to reveal their strengths and limitations. One of the goals of this report is to help people to understand the scientific data, including the logic behind the scientific conclusions, so it goes into greater detail than previous reports on the subject. In many cases, we have explained why particular studies are inconclusive and what sort of evidence is needed to support particular claims about the harms or benefits attributed to marijuana. Ideally, this report will enable the thoughtful reader to interpret new information about marijuana that will continue to emerge rapidly well after this report is published.

Can marijuana relieve health problems? Is it safe for medical use? Those straightforward questions are embedded in a web of social concerns, which lie outside the scope of this report. Controversies concerning nonmedical use of marijuana spill over onto the medical marijuana debate and tend to obscure the real state of scientific knowledge. In contrast

with the many disagreements bearing on the social issues, the study team found substantial consensus, among experts in the relevant disciplines, on the scientific evidence bearing on potential medical use. This report analyzes science, not the law. As in any policy debate, the value of scientific analysis is that it can provide a foundation for further discussion. Distilling scientific evidence does not in itself solve a policy problem. What it can do is illuminate the common ground, bringing to light fundamental differences out of the shadows of misunderstanding and misinformation that currently prevail. Scientific analysis cannot be the end of the debate, but it should at least provide the basis for an honest and informed discussion.

Our analysis of the evidence and arguments concerning the medical use of marijuana focuses on the strength of the supporting evidence and does not refer to the motivations of people who put forth the evidence and arguments. That is, it is not relevant to scientific validity whether an argument is put forth by someone who believes that all marijuana use should be legal or by someone who believes that any marijuana use is highly damaging to individual users and to society as a whole. Nor does this report comment on the degree to which scientific analysis is compatible with current regulatory policy. Although many have argued that current drug laws pertaining to marijuana are inconsistent with scientific data, it is important to understand that decisions about drug regulation are based on a variety of moral and social considerations, as well as on medical and scientific ones.

Even when a drug is used only for medical purposes, value judgments affect policy decisions concerning its medical use. For example, the magnitude of a drug's expected medical benefit affects regulatory judgments about the acceptability of risks associated with its use. Also, although a drug is normally approved for medical use only on proof of its "safety and efficacy," patients with life-threatening conditions are sometimes (under protocols for "compassionate use") allowed access to unapproved drugs whose benefits and risks are uncertain. Value judgments play an even more substantial role in regulatory decisions concerning drugs, such as marijuana, that are sought and used for nonmedical purposes. Then policymakers must take into account not only the risks and benefits associated with medical use but also possible interactions between the regulatory arrangements governing medical use and the integrity of the legal controls set up to restrict nonmedical use.

It should be clear that many elements of drug control policy lie outside the realm of biology and medicine. Ultimately, the complex moral and social judgments that underlie drug control policy must be made by the American people and their elected officials. A goal of this report is to

evaluate the biological and medical factors that should be taken into account in making those judgments.

HOW THIS STUDY WAS CONDUCTED

Information was gathered through scientific workshops, site visits, analysis of the relevant scientific literature, and extensive consultation with biomedical and social scientists. The three 2-day workshops—in Irvine, California; New Orleans, Louisiana; and Washington, D.C.—were open to the public and included scientific presentations and reports, mostly from patients and their families, about their experiences with and perspectives on the medical use of marijuana. Scientific experts in various fields were selected to talk about the latest research on marijuana, cannabinoids, and related topics (listed in Appendix B). Selection of the experts was based on recommendations by their peers, who ranked them among the most accomplished scientists and the most knowledgeable about marijuana and cannabinoids in their own fields. In addition, advocates for (John Morgan) and against (Eric A. Voth) the medical use of marijuana were invited to present scientific evidence in support of their positions.

Information presented at the scientific workshops was supplemented by analysis of the scientific literature and evaluating the methods used in various studies and the validity of the authors' conclusions. Different kinds of clinical studies are useful in different ways: results of a controlled double-blind study with adequate sample sizes can be expected to apply to the general population from which study subjects were drawn; an isolated case report can suggest further studies but cannot be presumed to be broadly applicable; and survey data can be highly informative but are generally limited by the need to rely on self-reports of drug use and on unconfirmed medical diagnoses. This report relies mainly on the most relevant and methodologically rigorous studies available and treats the results of more limited studies cautiously. In addition, study results are presented in such a way as to allow thoughtful readers to judge the results themselves.

The Institute of Medicine (IOM) appointed a panel of nine experts to advise the study team on technical issues. These included neurology and the treatment of pain (Howard Fields); regulation of prescription drugs (J. Richard Crout); AIDS wasting and clinical trials (Judith Feinberg); treatment and pathology of multiple sclerosis (Timothy Vollmer); drug dependence among adolescents (Thomas Crowley); varieties of drug dependence (Dorothy Hatsukami); internal medicine, health care delivery, and clinical epidemiology (Eric B. Larson); cannabinoids and marijuana pharmacology (Billy R. Martin); and cannabinoid neuroscience (Steven R. Childers).

Public outreach included setting up a Web site that provided information about the study and asked for input from the public. The Web site was open for comment from November 1997 until November 1998. Some 130 organizations were invited to participate in the public workshops. Many people in the organizations—particularly those opposed to the medical use of marijuana—felt that a public forum was not conducive to expressing their views; they were invited to communicate their opinions (and reasons for holding them) by mail or telephone. As a result, roughly equal numbers of persons and organizations opposed to and in favor of the medical use of marijuana were heard from.

The study team visited four cannabis buyers' clubs in California (the Oakland Cannabis Buyers' Cooperative, the San Francisco Cannabis Cultivators Club, the Los Angeles Cannabis Resource Center, and Californians Helping Alleviate Medical Problems, or CHAMPS) and two HIV/AIDS clinics (AIDS Health Care Foundation in Los Angeles and Louisiana State University Medical Center in New Orleans). We listened to many individual stories from the buyers' clubs about using marijuana to treat a variety of symptoms and heard clinical observations on the use of Marinol to treat AIDS patients. Marinol is the brand name for dronabinol, which is Δ^9 -tetrahydrocannabinol (THC) in pill form and is available by prescription for the treatment of nausea associated with chemotherapy and AIDS wasting.

MARIJUANA TODAY

The Changing Legal Landscape

In the 20th century, marijuana has been used more for its euphoric effects than as a medicine. Its psychological and behavioral effects have concerned public officials since the drug first appeared in the southwestern and southern states during the first two decades of the century. By 1931, at least 29 states had prohibited use of the drug for nonmedical purposes.³ Marijuana was first regulated at the federal level by the Marijuana Tax Act of 1937, which required anyone producing, distributing, or using marijuana for medical purposes to register and pay a tax and which effectively prohibited nonmedical use of the drug. Although the act did not make medical use of marijuana illegal, it did make it expensive and inconvenient. In 1942, marijuana was removed from the U.S. Pharmacopoeia because it was believed to be a harmful and addictive drug that caused psychoses, mental deterioration, and violent behavior.

In the late 1960s and early 1970s, there was a sharp increase in marijuana use among adolescents and young adults. The current legal status of marijuana was established in 1970 with the passage of the Controlled

Medical Marijuana Legislation Among the States

The 1996 California referendum known as Proposition 215 allowed seriously ill Californians to obtain and use marijuana for medical purposes without criminal prosecution or sanction. A physician's recommendation is needed. Under the law, physicians cannot be punished or denied any right or privilege for recommending marijuana to patients who suffer from any illness for which marijuana will provide relief.

The 1996 Arizona referendum known as Proposition 200 was largely about prison reform but also gave physicians the option to prescribe controlled substances, including those in Schedule I (e.g., marijuana), to treat the disease or relieve the suffering of seriously or terminally ill patients. Five months after the referendum was passed, it was stalled when Arizona legislators voted that all prescription medications must be approved by the Food and Drug Administration, and marijuana is not so approved. In November 1998, Arizona voters passed a second referendum designed to allow physician's to prescribe marijuana as medicine, but this is still at odds with federal law.⁸

As of summer 1998, eight states—California, Connecticut, Louisiana, New Hampshire, Ohio, Vermont, Virginia, and Wisconsin—had laws that permit physicians to prescribe marijuana for medical purposes or to allow a medical necessity defense.⁸ In November 1998, five states—Arizona, Alaska, Oregon, Nevada, and Washington—passed medical marijuana ballot initiatives. The District of Columbia also voted on a medical marijuana initiative, but was barred from counting the votes because an amendment designed to prohibit them from doing so was added to the federal appropriations bill; however, exit polls suggested that a majority of voters had approved the measure.

Substances Act, which divided drugs into five schedules and placed marijuana in Schedule I, the category for drugs with high potential for abuse and no accepted medical use (see Appendix C, Scheduling Definitions). In 1972, the National Organization for the Reform of Marijuana Legislation (NORML), an organization that supports decriminalization of marijuana, unsuccessfully petitioned the Bureau of Narcotics and Dangerous Drugs to move marijuana from Schedule I to Schedule II. NORML argued that marijuana is therapeutic in numerous serious ailments, less toxic, and in many cases more effective than conventional medicines.¹³ Thus, for 25 years the medical marijuana movement has been closely linked with the marijuana decriminalization movement, which has colored the debate. Many people criticized that association in their letters to IOM and during the public workshops of this study. The argument against the medical use

of marijuana presented most often to the IOM study team was that “the medical marijuana movement is a Trojan horse”; that is, it is a deceptive tactic used by advocates of marijuana decriminalization who would exploit the public’s sympathy for seriously ill patients.

Since NORML’s petition in 1972, there have been a variety of legal decisions concerning marijuana. From 1973 to 1978, 11 states adopted statutes that decriminalized use of marijuana, although some of them recriminalized marijuana use in the 1980s and 1990s. During the 1970s, reports of the medical value of marijuana began to appear, particularly claims that marijuana relieved the nausea associated with chemotherapy. Health departments in six states conducted small studies to investigate the reports. When the AIDS epidemic spread in the 1980s, patients found that marijuana sometimes relieved their symptoms, most dramatically those associated with AIDS wasting. Over this period a number of defendants charged with unlawful possession of marijuana claimed that they were using the drug to treat medical conditions and that violation of the law was therefore justified (the so-called medical necessity defense). Although most courts rejected these claims, some accepted them.⁸

Against that backdrop, voters in California and Arizona in 1996 passed two referenda that attempted to legalize the medical use of marijuana under particular conditions. Public support for patient access to marijuana for medical use appears substantial; public opinion polls taken during 1997 and 1998 generally reported 60–70 percent of respondents in favor of allowing medical uses of marijuana.¹⁵ However, those referenda are at odds with federal laws regulating marijuana, and their implementation raises complex legal questions.

Despite the current level of interest, referenda and public discussions have not been well informed by carefully reasoned scientific debate. Although previous reports have all called for more research, the nature of the research that will be most helpful depends greatly on the specific health conditions to be addressed. And while there have been important recent advances in our understanding of the physiological effects of marijuana, few of the recent investigators have had the time or resources to permit detailed analysis. The results of those advances, only now beginning to be explored, have significant implications for the medical marijuana debate.

Several months after the passage of the California and Arizona medical marijuana referendums, the Office of National Drug Control Policy (ONDCP) asked whether IOM would conduct a scientific review of the medical value of marijuana and its constituent compounds. In August 1997, IOM formally began the study and appointed John A. Benson Jr. and Stanley J. Watson Jr. to serve as principal investigators for the study.

The charge to IOM was to review the medical use of marijuana and the harms and benefits attributed to it (details are given in Appendix D).

MARIJUANA AND MEDICINE

Marijuana plants have been used since antiquity for both herbal medication and intoxication. The current debate over the medical use of marijuana is essentially a debate over the value of its medicinal properties relative to the risk posed by its use.

Marijuana's use as an herbal remedy before the 20th century is well documented.^{1,10,11} However, modern medicine adheres to different standards from those used in the past. The question is not whether marijuana can be used as an herbal remedy but rather how well this remedy meets today's standards of efficacy and safety. We understand much more than previous generations about medical risks. Our society generally expects its licensed medications to be safe, reliable, and of proven efficacy; contaminants and inconsistent ingredients in our health treatments are not tolerated. That refers not only to prescription and over-the-counter drugs but also to vitamin supplements and herbal remedies purchased at the grocery store. For example, the essential amino acid *l*-tryptophan was widely sold in health food stores as a natural remedy for insomnia until early 1990 when it became linked to an epidemic of a new and potentially fatal illness (eosinophilia-myalgia syndrome).^{9,12} When it was removed from the market shortly thereafter, there was little protest, despite the fact that it was safe for the vast majority of the population. The 1,536 cases and 27 deaths were later traced to contaminants in a batch produced by a single Japanese manufacturer.

Although few herbal medicines meet today's standards, they have provided the foundation for modern Western pharmaceuticals. Most current prescriptions have their roots either directly or indirectly in plant remedies.⁷ At the same time, most current prescriptions are synthetic compounds that are only distantly related to the natural compounds that led to their development. Digitalis was discovered in foxglove, morphine in poppies, and taxol in the yew tree. Even aspirin (acetylsalicylic acid) has its counterpart in herbal medicine: for many generations, American Indians relieved headaches by chewing the bark of the willow tree, which is rich in a related form of salicylic acid.

Although plants continue to be valuable resources for medical advances, drug development is likely to be less and less reliant on plants and more reliant on the tools of modern science. Molecular biology, bioinformatics software, and DNA array-based analyses of genes and chemistry are all beginning to yield great advances in drug discovery and development. Until recently, drugs could only be *discovered*; now they can

be *designed*. Even the discovery process has been accelerated through the use of modern drug-screening techniques. It is increasingly possible to identify or isolate the chemical compounds in a plant, determine which compounds are responsible for the plant's effects, and select the most effective and safe compounds—either for use as purified substances or as tools to develop even more effective, safer, or less expensive compounds.

Yet even as the modern pharmacological toolbox becomes more sophisticated and biotechnology yields an ever greater abundance of therapeutic drugs, people increasingly seek alternative, low-technology therapies.^{4,5} In 1997, 46 percent of Americans sought nontraditional medicines and spent over 27 billion unreimbursed dollars; the total number of visits to alternative medicine practitioners appears to have exceeded the number of visits to primary care physicians.^{5,6} Recent interest in the medical use of marijuana coincides with this trend toward self-help and a search for “natural” therapies. Indeed, several people who spoke at the IOM public hearings in support of the medical use of marijuana said that they generally preferred herbal medicines to standard pharmaceuticals. However, few alternative therapies have been carefully and systematically tested for safety and efficacy, as is required for medications approved by the FDA (Food and Drug Administration).²

WHO USES MEDICAL MARIJUANA?

There have been no comprehensive surveys of the demographics and medical conditions of medical marijuana users, but a few reports provide some indication. In each case, survey results should be understood to reflect the situation in which they were conducted and are not necessarily characteristic of medical marijuana users as a whole. Respondents to surveys reported to the IOM study team were all members of “buyers’ clubs,” organizations that provide their members with marijuana, although not necessarily through direct cash transactions. The atmosphere of the marijuana buyers’ clubs ranges from that of the comparatively formal and closely regulated Oakland Cannabis Buyers’ Cooperative to that of a “country club for the indigent,” as Denis Peron described the San Francisco Cannabis Cultivators Club (SFCCC), which he directed.

John Mendelson, an internist and pharmacologist at the University of California, San Francisco (UCSF) Pain Management Center, surveyed 100 members of the SFCCC who were using marijuana at least weekly. Most of the respondents were unemployed men in their forties. Subjects were paid \$50 to participate in the survey; this might have encouraged a greater representation of unemployed subjects. All subjects were tested for drug use. About half tested positive for marijuana only; the other half tested positive for drugs in addition to marijuana (23% for cocaine and 13% for

TABLE 1.1 Self-Reported Disorders Treated with Marijuana by Members of San Francisco Cannabis Cultivators Club

Disorder	No. of Subjects
HIV	60
Musculoskeletal disorders and arthritis	39
Psychiatric disorders (primarily depression)	27
Neurological disorders and nonmusculoskeletal pain syndromes	9
Gastrointestinal disorders (most often nausea)	7
Other disorders	
Glaucoma, allergies, nephrolithiasis, and the skin manifestations of Reiter syndrome	7
Total disorders	149
Total number of respondents	100

amphetamines). The predominant disorder was AIDS, followed by roughly equal numbers of members who reported chronic pain, mood disorders, and musculoskeletal disorders (Table 1.1).

The membership profile of the San Francisco club was similar to that of the Los Angeles Cannabis Resource Center (LACRC), where 83% of the 739 patients were men, 45% were 36–45 years old, and 71% were HIV positive. Table 1.2 shows a distribution of conditions somewhat different from that in SFCCC respondents, probably because of a different membership profile. For example, cancer is generally a disease that occurs late in life; 34 (4.7%) of LACRC members were over 55 years old; only 2% of survey respondents in the SFCCC study were over 55 years old.

Jeffrey Jones, executive director of the Oakland Cannabis Buyers' Cooperative, reported that its largest group of patients is HIV-positive men in their forties. The second-largest group is patients with chronic pain.

Among the 42 people who spoke at the public workshops or wrote to the study team, only six identified themselves as members of marijuana buyers' clubs. Nonetheless, they presented a similar profile: HIV/AIDS was the predominant disorder, followed by chronic pain (Tables 1.3 and 1.4). All HIV/AIDS patients reported that marijuana relieved nausea and vomiting and improved their appetite. About half the patients who reported using marijuana for chronic pain also reported that it reduced nausea and vomiting.

Note that the medical conditions referred to are only those reported to the study team or to interviewers; they cannot be assumed to represent complete or accurate diagnoses. Michael Rowbotham, a neurologist at the UCSF Pain Management Center, noted that many pain patients referred

TABLE 1.2 Self-Reported Disorders Treated with Marijuana by Members of Los Angeles Cannabis Resource Center (LACRC), According to Center Staff^a

Treated Disorder	No. of Subjects	% of Subjects
HIV ^b	528	71
Cancer	40	5.4
Terminal cancer	10	1.4
Mood disorders (depression)	4	0.5
Musculoskeletal (multiple sclerosis, arthritis)	30	4.1
Chronic pain and back pain	33	4.5
Gastrointestinal	7	2.3
Neurological disorders (epilepsy, Tourette syndrome, brain trauma)	7	0.9
Seizures or migraines ^c	13	1.8
Glaucoma	15	2.0
Miscellaneous	42	5.7
Total number	739	100

^aResults are based on a review of 739 individual records by LACRC staff members. In contrast with Mendelson's survey of San Francisco Cannabis Cultivators Club (Table 1.1), only the primary disorder is indicated here. Membership in LACRC is contingent on a doctor's letter of acknowledgment, but diagnoses are not independently confirmed.

^bHIV patients use marijuana to control nausea, increase appetite (to combat wasting), and relieve gastrointestinal distress caused by AIDS medications. These uses are not indicated separately.

^cAs described by LACRC staff, some of these cases might also be neurological disorders.

to that center arrive with incorrect diagnoses or with pain of unknown origin. At that center the patients who report medical benefit from marijuana say that it does not reduce their pain but enables them to cope with it.

Most—not all—people who use marijuana to relieve medical conditions have previously used it recreationally. An estimated 95% of the LACRC members had used marijuana before joining the club. It is important to emphasize the absence of comprehensive information on marijuana use before its use for medical conditions. Frequency of prior use almost certainly depends on many factors, including membership in a buyers' club, membership in a population sector that uses marijuana more often than others (for example, men 20–30 years old), and the medical condition being treated with marijuana (for example, there are probably relatively fewer recreational marijuana users among cancer patients than among AIDS patients).

TABLE 1.3 Summary of Reports to IOM Study Team by 43 Individuals

Symptoms	Dominant Disease	Symptoms	Dominant Disease
Anorexia, nausea, vomiting	AIDS	Pain	Migraine
	AIDS		Injury
	AIDS		Injury
	AIDS		Epilepsy and postpolio syndrome
	AIDS		Trauma and epilepsy
	AIDS		Degenerative disk disease
	AIDS		Rheumatoid arthritis
	AIDS and cancer		Nail-patella syndrome
	Cancer		Reflex sympathetic dystrophy
	Testicular cancer		Gulf War chemical exposure
	Cancer and multiple sclerosis		Multiple congenital cartilaginous exostosis
	Thyroid condition ^a		Histiocytosis X
	Migraine		
Wilson’s disease			
Mood disorders	Depression	Muscle spasticity	Spasticity ^a
	Depression		Multiple sclerosis
	Depression and anxiety		Multiple sclerosis
	Depression and anxiety		Multiple sclerosis
	Manic depression		Paralysis
			Spinal-cord injury
			Spasmodic torticollis
		Intraocular pressure	Glaucoma
		Diarrhea	Crohn’s disease

^aNot specified.

NOTE: This table lists the people who reported to the IOM study team during the public workshops, or through letters, that they use marijuana as medicine; it should not be interpreted as a representative sample of the full spectrum of people who use marijuana as medicine. Each dominant disease represents an individual report.

Patients who reported their experience with marijuana at the public workshops said that marijuana provided them with great relief from symptoms associated with disparate diseases and ailments, including AIDS wasting, spasticity from multiple sclerosis, depression, chronic pain, and nausea associated with chemotherapy. Their circumstances and symptoms were varied, and the IOM study team was not in a position to make medical evaluations or confirm diagnoses. Three representative cases presented to the IOM study team are presented in Box 1.1; the stories have been edited for brevity, but each case is presented in the patient’s words and with the patient’s permission.

TABLE 1.4 Primary Symptoms of 43 Individuals Who Reported to IOM Study Team

Primary Symptom	Symptom Frequency		Multiple Symptoms	
	No. of Reports ^a	% of Total Symptoms Reported	No. Who Reported (primary) Additional Symptoms	% of Those Who Reported Primary Symptoms
Anorexia, nausea, vomiting	21	31	13	62
Diarrhea	4	6	3	75
Intraocular pressure	2	3	1	50
Mood disorders	12	18	7	58
Muscle spasticity	12	18	7	58
Pain	16	24	13	81
Total	67		44	66

^aForty-three persons reporting; 20 reported relief from more than one symptom.

The variety of stories presented left the study team with a clear view of people's beliefs about how marijuana had helped them. But this collection of anecdotal data, although useful, is limited. We heard many positive stories but no stories from people who had tried marijuana but found it ineffective. This is a fraction with an unknown denominator. For the numerator we have a sample of positive responses; for the denominator we have no idea of the total number of people who have tried marijuana for medical purposes. Hence, it is impossible to estimate the clinical value of marijuana or cannabinoids in the general population based on anecdotal reports. Marijuana clearly seems to relieve some symptoms for some people—even if only as a placebo effect. But what is the balance of harmful and beneficial effects? That is the essential medical question that can be answered only by careful analysis of data collected under controlled conditions.

CANNABIS AND THE CANNABINOIDS

Marijuana is the common name for *Cannabis sativa*, a hemp plant that grows throughout temperate and tropical climates. The most recent review of the constituents of marijuana lists 66 cannabinoids (Table 1.5).¹⁶ But that does not mean there are 66 different cannabinoid effects or interactions. Most of the cannabinoids are closely related; they fall into only 10

TABLE 1.5 Cannabinoids Identified in Marijuana

Cannabinoid Group	Common Abbreviation	No. of Known Variants in Each Group
Δ^9 -Tetrahydrocannabinol	Δ^9 -THC	9
Δ^8 -Tetrahydrocannabinol	Δ^8 -THC	2
Cannabichromene	CBC	5
Cannabicyclol	CBL	3
Cannabidiol	CBD	7
Cannabielsoin	CBE	5
Cannabigerol	CBG	6
Cannabinidiol	CBND	2
Cannabinol	CBN	7
Cannabitriol	CBT	9
Miscellaneous types		11
Total		66

groups of closely related cannabinoids, many of which differ by only a single chemical moiety and might be midpoints along biochemical pathways—that is, degradation products, precursors, or byproducts.^{16,18} Δ^9 -tetrahydrocannabinol (Δ^9 -THC) is the primary psychoactive ingredient; depending on the particular plant, either THC or cannabidiol is the most abundant cannabinoid in marijuana (Figure 1.1). Throughout this report, THC is used to indicate Δ^9 -THC. In the few cases where variants of THC are discussed, the full names are used. All the cannabinoids are lipophilic—they are highly soluble in fatty fluids and tissues but not in water. Indeed, THC is so lipophilic that it is aptly described as “greasy.”

Throughout this report, *marijuana* refers to unpurified plant extracts, including leaves and flower tops, regardless of how they are consumed—whether by ingestion or by smoking. References to the effects of marijuana should be understood to include the composite effects of its various components; that is, the effects of THC are included among the effects of marijuana, but not all the effects of marijuana are necessarily due to THC. Discussions concerning *cannabinoids* refer only to those particular compounds and not to the plant extract. This distinction is important; it is often blurred or exaggerated.

Cannabinoids are produced in epidermal glands on the leaves (especially the upper ones), stems, and the bracts that support the flowers of the marijuana plant. Although the flower itself has no epidermal glands, it has the highest cannabinoid content anywhere on the plant, probably because of the accumulation of resin secreted by the supporting bracteole

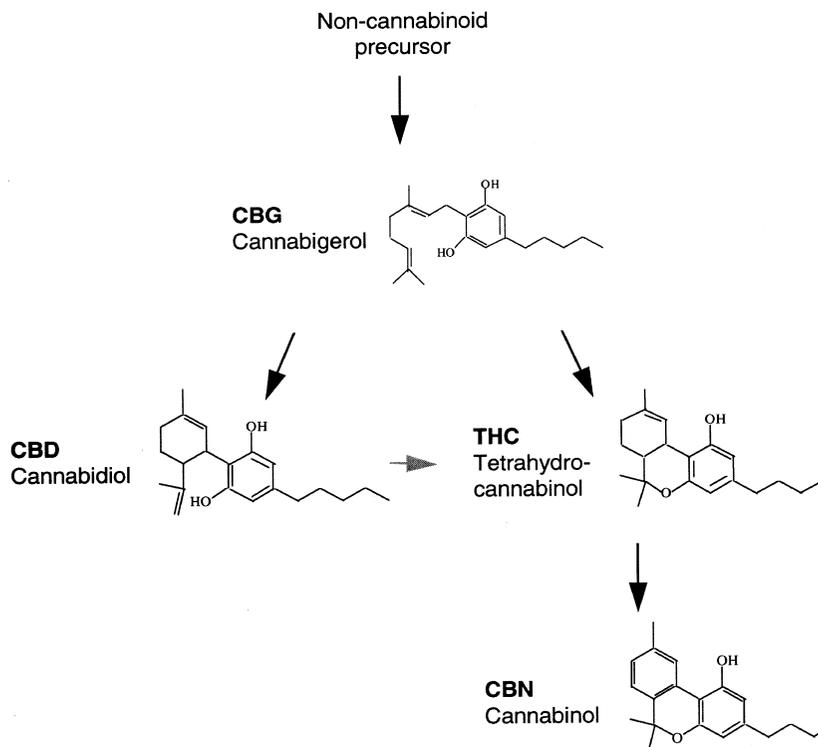


FIGURE 1.1 Cannabinoid biosynthesis. Arrows indicate cannabinoid biosynthesis pathway; dark arrows indicate established pathways; the light gray arrow indicates a probable but not well-established pathway (R. Mechoulam, Hebrew University, personal communication, 1999).¹¹ The great majority of studies reporting on the effects of cannabinoids refer to THC; most of the rest are about CBD and CBN. Other cannabinoids found in marijuana do not appear to play an important role in the drug's effects.

(the small leaf-like part below the flower). The amounts of cannabinoids and their relative abundance in a marijuana plant vary with growing conditions, including humidity, temperature, and soil nutrients (reviewed in Pate, 1994¹⁴). The chemical stability of cannabinoids in harvested plant material is also affected by moisture, temperature, sunlight, and storage. They degrade under any storage condition.

BOX 1.1 Selected Cases from the Public Sessions

G.S. spoke at the IOM workshop in Louisiana about his use of marijuana first to combat AIDS wasting syndrome and later for relief from the side effects of AIDS medications.

Skin rashes, dry mouth, foul metallic aftertaste, numbness of the face, swelling of the limbs, fever spikes, headaches, dizziness, anemia, clinical depression, neuropathy so crippling that I could not type, so painful that the bed sheets felt like sandpaper, nausea so severe that I sometimes had to leave the dinner table to vomit, and diarrhea so unpredictable that I dared not leave the house without diapers.

These are some of the horrors that I have endured in the past 10 years during my fight for life against the human immunodeficiency virus. But these ravages were not caused by HIV itself, or by any of the opportunistic infections that mark the steady progression of AIDS. Each of these nightmares was a side effect of one of the hundreds of medications I have taken to fight one infection after another on my way to a seemingly certain early grave.

Had you known me three years ago, you would not recognize me now. After years of final-stage AIDS, I had wasted to 130 lb. The purple Kaposi's sarcoma lesions were spreading. The dark circles under my eyes told of sleepless nights and half-waking days. I encountered passages of time marked by medication schedules, nausea, and diarrhea. I knew that I was dying. Every reflection shimmered with death, my ghost-like pallor in the mirror, the contained terror on the face of a bus passenger beside me, and most of all the resigned sadness in my mother's eyes.

But still I was fortunate because along the way I rediscovered the ancient understanding of marijuana's medicinal benefit. So I smoked pot. Every day. The pot calmed my stomach against handfuls of pills. The pot made me hungry so that I could eat without a tube. The pot eased the pain of crippling neural side effects so that I could dial the phone by myself. The pot calmed my soul and allowed me to accept that I would probably die soon. Because I smoked pot I lived long enough to see the development of the first truly effective HIV therapies. I lived to gain 50 lb., regain my vigor, and celebrate my 35th birthday. I lived to sit on the bus without frightening the passenger beside me.

Even at this stage of my recovery I take a handful of pills almost every day and will probably continue to do so for the rest of my life. While I am grateful for the life-saving protease inhibitor therapies, they bring with them a host of adverse reactions and undesirable side effects. Different patients experience different reactions, of course, but almost all patients experience some. Smoking marijuana relieves many of these side effects.

I am not one of the exceptional eight patients in the United States with

Continued

legal permission to smoke marijuana. Every day I risk arrest, property forfeiture, fines, and imprisonment. But I have no choice, you see, just as I have no choice but to endure the side effects of these toxic medications. So, many patients like me are breaking the law to enjoy relief that no other therapy provides.

I sit here, I believe, as living proof that marijuana can have a beneficial effect in staving off wasting. Every pound was a day. I figured that for every pound of body weight I could maintain, that was another day that I could live in hopes that some effective therapy would emerge.

* * *

B.D. spoke at the IOM workshop in Louisiana. She is one of eight patients who are legally allowed to smoke marijuana under a Compassionate Use Protocol. She uses marijuana to relieve nausea, muscle spasticity, and pain associated with multiple sclerosis.

I was diagnosed with multiple sclerosis in 1988. Prior to that, I was an active person with ballet and swimming. I now have a swimming pool, so I swim each and every day, and I smoke marijuana. The government has given me the marijuana to smoke. Each month I pick up a can filled with the marijuana cigarettes rolled by the government.

At one time I weighed 85 lb. and I now weigh 105. Twenty pounds is quite a bit to put on. I could not walk. I did not have the appetite. I use a scooter now for distance. I can get around the house. I have a standard poodle who is kind of like an assistant dog. She is good at it. She helps me.

When I found out that there was a program to get marijuana from the government, I decided that was the answer. I was not a marijuana smoker before that. In fact, I used to consider the people I knew who smoked the marijuana as undesirables. Now, I myself am an undesirable.

But it works. It takes away the backache. With multiple sclerosis, you can get spasms, and your leg will just go straight out and you cannot stop that leg. You may have danced all of your life and put the leg where you wanted it to be, but the MS takes that from you. So I use the swimming pool, and that helps a lot. The kicks are much less when I have smoked a marijuana cigarette. Since 1991, I've smoked 10 cigarettes a day. I do not take any other drugs. Marijuana seems to have been my helper. At one time, I did not think much of the people who smoke it. But when it comes to your health, it makes a big difference.

* * *

J.H. spoke at the IOM workshop in Washington, D.C. He was seriously injured in an accident, suffers from a form of arthritis associated with abnormal activity of the sympathetic nervous system known as reflex sympathetic dystrophy, and has hepatitis C. He uses marijuana to relieve nausea from liver disease, pain, and muscle spasms.

I am 48 years old, married with two children. I am a veteran who served during the Vietnam war. I was exposed to hepatitis C in 1972 by a blood

transfusion, which I needed because of a motor vehicle accident that broke my back; ruined my right shoulder, my left thumb, and hand; and almost amputated my right leg at the knee. My hepatitis C was not diagnosed until 1997—after the disease had destroyed my pancreas* and I had four heart attacks, one angioplasty, and a minor stroke. In 1989, while at work, I was involved in an accident with a large soil survey auger. My pelvis was crushed, and serious nerve damage was the result. I also have reflex sympathetic dystrophy, which is a neurological disease that has a tremendous amount of pain and muscle spasms.

I have reached what the doctors call end-stage liver disease from the hepatitis C. I have lost 85 lbs. due to the severe bouts of nausea and vomiting. Every time I come home from a hospital stay, my 7 year old asks if I got the liver transplant. I am on a transplant list, but I am not a candidate until I am seven days from death.

In October 1997, after trying four different anti-nausea medications, four of the doctors that I see told me to go to Europe and see a doctor and try medicinal cannabis. My primary care doctor wrote me a letter to carry with my medical records asking that the doctor help me in any way that he could to alleviate the symptoms of the hepatitis C and the reflex sympathetic dystrophy. Those symptoms are severe nausea and pain from the hepatitis C and pain and muscle spasms from the neurological disease.

I went to Europe in November 1997, where I saw a doctor of internal medicine. He prescribed me cannabis, 1–2 g a day. I got the medicine and a pipe and tried it. Within two minutes of taking two puffs from the pipe, the nausea was gone. I don't think that I felt the high, although I was quite elated. In about 45 min. I was starving. Normally, I have a fear of eating because I vomit almost always after I eat or take a pill. I forgot about that, and I think I ate more that night than I had eaten in months. I did feel a little nauseated after about four hours, but I smoked two more puffs, and in about two hours I went to bed. The next morning I felt hungry. During my nine-day stay in Europe, I was able to stay free of vomiting and the waves of nausea became less frequent.

I had experienced four years of pain control using Tegretol, a drug used by epileptics to control seizures. Now I can't use that medication because of the damage that it causes my cirrhotic liver. When I smoked about 2 g of marijuana a day, the nausea was gone and I was no longer losing weight. The pain was at an acceptable level. Sometimes I still find it necessary to use an opiate painkiller, but only when the pain is at its worst. Surprisingly, I lost an associated high within a few days. I also think the cannabis has an antidepressant effect on me, as I no longer have what I call the "poor me" feelings that I experienced after learning about the hepatitis C.

*This is an unlikely consequence of hepatitis C; it is more likely that the patient's liver was damaged.

ORGANIZATION OF THE REPORT

Throughout the report, steps that might be taken to fill the gaps in understanding both the potential harms and benefits of marijuana and cannabinoid use are identified. Those steps include identifying knowledge gaps, promising research directions, and potential therapies based on scientific advances in cannabinoid biology.

Chapter 2 reviews basic cannabinoid biology and provides a foundation to understand the medical value of marijuana or its constituent cannabinoids. In consideration of the physician's first rule, "first, do no harm," the potential harms attributed to the medical use of marijuana are reviewed before the potential medical benefits. Chapter 3 reviews the risks posed by marijuana use, with emphasis on medical use.

Chapter 4 analyzes the most credible clinical data relevant to the medical use of marijuana. It reviews what is known about the physiological mechanisms underlying particular conditions (for example, chronic pain, vomiting, anorexia, and muscle spasticity), what is known about the cellular actions of cannabinoids, and the levels of proof needed to show that marijuana is an effective treatment for specific symptoms. It does not analyze the historical literature; history is informative in enumerating uses of marijuana, but it does not provide the sort of information needed for a scientifically sound evaluation of the efficacy and safety of marijuana for clinical use. Because marijuana is advocated primarily as affording relief from the symptoms of disease rather than as a cure, this chapter is organized largely by symptoms as opposed to disease categories. Finally, chapter 4 compares the conclusions of this report with those of other recent reports on the medical use of marijuana.

Chapter 5 describes the process of and analyzes the prospects for cannabinoid drug development.

REFERENCES

1. Abel EL. 1980. *Marijuana: The First Twelve Thousand Years*. New York: Plenum Press.
2. Angell M, Kassirer JP. 1998. Alternative medicine—The risks of untested and unregulated remedies. *New England Journal of Medicine* 339:839–841.
3. Bonnie RJ, Whitebread II CH. 1974. *The Marihuana Conviction: A History of Marihuana Prohibition in the United States*. Charlottesville, VA: University Press of Virginia.
4. Eisenberg DM. 1997. Advising patients who seek alternative medical therapies. *Annals of Internal Medicine* 127:61–69.
5. Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, Kessler RC. 1998. Trends in alternative medicine use in the United States, 1990–1997: Results of a follow-up national survey. *Journal of the American Medical Association* 280:1569–1575.
6. Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. 1993. Unconventional medicine in the United States: Prevalence, costs, and patterns of use. *New England Journal of Medicine* 328:246–252.

7. Grifo F, Newman D, Fairfield A, Bhattacharya B, Grupenhoff JT. 1997. The origins of prescription drugs. In: Grifo F, Rosenthal J, Editors. *Biodiversity and Human Health*. Washington, DC: Island Press. Pp. 131–163.
8. Herstek J. 1998. *Behavioral Health Issue Briefs. Medical Marijuana*. Washington, DC: Health Policy Tracking Service, National Conference of State Legislatures.
9. Kilbourne EM, Philen RM, Kamb ML, Falk H. 1996. Tryptophan produced by *Showa Denko* and epidemic eosinophilia-myalgia syndrome. *Journal of Rheumatology Supplement* 46:81–88. Comment on: *Journal of Rheumatology Supplement* 1996 46:44–58 and 60–72; discussion 58–59.
10. Mathre ML, Editor. 1997. *Cannabis in Medical Practice*. Jefferson, NC: MacFarland and Co.
11. Mechoulam R. 1986. The pharmacohistory of *Cannabis Sativa*. In: Mechoulam R, Editor. *Cannabinoids as Therapeutic Agents*. Boca Raton, FL: CRC Press. Pp. 1–19.
12. Milburn DS, Myers CW. 1991. Tryptophan toxicity: A pharmacoepidemiologic review of eosinophilia-myalgia syndrome. *DICP* 25:1259–1262.
13. NORML. The Medical Use of Marijuana [WWW document]. URL <http://norml.org/medical/index.html> (accessed July 9, 1998).
14. Pate DW. 1994. Chemical ecology of cannabis. *Journal of the International Hemp Association* 1:29, 32–37.
15. Peterson K. 15 January 1997. Notes: Weighing in on a medical controversy; *USA Today's* Baby Boomer Panel. *USA Today*, p. 12D.
16. Ross SA, Elsohly MA. 1995. Constituents of *Cannabis sativa* L. XXVIII. A review of the natural constituents: 1980–1994. *Zagazig Journal for Pharmaceutical Sciences* 4:1–10.
17. Taura F, Morimoto S, Shoyama Y. 1995. First direct evidence for the mechanism of delta 1-tetrahydrocannabinolic acid biosynthesis. *Journal of the American Chemical Society* 117:9766–9767.
18. Turner CE, Elsohly MA, Boeren EG. 1980. Constituents of *Cannabis sativa* L. XVII. A review of the natural constituents. *Journal of Natural Products* 43:169–234.

2

Cannabinoids and Animal Physiology



INTRODUCTION

Much has been learned since the publication of the 1982 Institute of Medicine (IOM) report *Marijuana and Health*.^{*} Although it was clear then that most of the effects of marijuana were due to its actions on the brain, there was little information about how THC acted on brain cells (neurons), which cells were affected by THC, or even what general areas of the brain were most affected by THC. Too little was known about cannabinoid physiology to offer any scientific insights into the harmful or therapeutic effects of marijuana. That is no longer true. During the past 16 years, there have been major advances in what basic science discloses about the potential medical benefits of cannabinoids, the group of compounds related to THC. Many variants are found in the marijuana plant, and other cannabinoids not found in the plant have been chemically synthesized. Sixteen years ago it was still a matter of debate as to whether THC acted nonspecifically by affecting the fluidity of cell membranes or whether a specific pathway of action was mediated by a receptor that responded selectively to THC (Table 2.1).

^{*}The field of neuroscience has grown substantially since the publication of the 1982 IOM report. The number of members in the Society for Neuroscience provides a rough measure of the growth in research and knowledge about the brain: as of the middle of 1998, there were over 27,000 members, more than triple the number in 1982.

TABLE 2.1 Landmark Discoveries Since the 1982 IOM Report

Year	Discovery	Primary Investigators
1986	Potent cannabinoid agonists are developed; they are the key to discovering the receptor.	M. R. Johnson and L. S. Melvin ⁷⁵
1988	First conclusive evidence of specific cannabinoid receptors.	A. Howlett and W. Devane ³⁶
1990	The cannabinoid brain receptor (CB ₁) is cloned, its DNA sequence is identified, and its location in the brain is determined.	L. Matsuda ¹⁰⁷ and M. Herkenham et al. ⁶⁰
1992	Anandamide is discovered—a naturally occurring substance in the brain that acts on cannabinoid receptors.	R. Mechoulam and W. Devane ³⁷
1993	A cannabinoid receptor is discovered outside the brain; this receptor (CB ₂) is related to the brain receptor but is distinct.	S. Munro ¹¹²
1994	The first specific cannabinoid antagonist, SR 141716A, is developed.	M. Rinaldi-Carmona ¹³²
1998	The first cannabinoid antagonist, SR144528, that can distinguish between CB ₁ and CB ₂ receptors discovered.	M. Rinaldi-Carmona ¹³³

Basic science is the wellspring for developing new medications and is particularly important for understanding a drug that has as many effects as marijuana. Even committed advocates of the medical use of marijuana do not claim that all the effects of marijuana are desirable for every medical use. But they do claim that the combination of specific effects of marijuana enhances its medical value. An understanding of those specific effects is what basic science can provide. The multiple effects of marijuana can be singled out and studied with the goals of evaluating the medical value of marijuana and cannabinoids in specific medical conditions, as well as minimizing unwanted side effects. An understanding of the basic mechanisms through which cannabinoids affect physiology permits more strategic development of new drugs and designs for clinical trials that are most likely to yield conclusive results.

Research on cannabinoid biology offers new insights into clinical use, especially given the scarcity of clinical studies that adequately evaluate the medical value of marijuana. For example, despite the scarcity of sub-

stantive clinical data, basic science has made it clear that cannabinoids can affect pain transmission and, specifically, that cannabinoids interact with the brain's endogenous opioid system, an important system for the medical treatment of pain (see chapter 4).

The cellular machinery that underlies the response of the body and brain to cannabinoids involves an intricate interplay of different systems. This chapter reviews the components of that machinery with enough detail to permit the reader to compare what is known about basic biology with the medical uses proposed for marijuana. For some readers that will be too much detail. Those readers who do not wish to read the entire chapter should, nonetheless, be mindful of the following key points in this chapter:

- The most far reaching of the recent advances in cannabinoid biology are the identification of two types of cannabinoid receptors (CB_1 and CB_2) and of anandamide, a substance naturally produced by the body that acts at the cannabinoid receptor and has effects similar to those of THC. The CB_1 receptor is found primarily in the brain and mediates the psychological effects of THC. The CB_2 receptor is associated with the immune system; its role remains unclear.
- The physiological roles of the brain cannabinoid system in humans are the subject of much active research and are not fully known; however, cannabinoids likely have a natural role in pain modulation, control of movement, and memory.
- Animal research has shown that the potential for cannabinoid dependence exists, and cannabinoid withdrawal symptoms can be observed. However, both appear to be mild compared to dependence and withdrawal seen with other drugs.
- Basic research in cannabinoid biology has revealed a variety of cellular pathways through which potentially therapeutic drugs could act on the cannabinoid system. In addition to the known cannabinoids, such drugs might include chemical derivatives of plant-derived cannabinoids or of endogenous cannabinoids such as anandamide but would also include noncannabinoid drugs that act on the cannabinoid system.

This chapter summarizes the basics of cannabinoid biology—as known today. It thus provides a scientific basis for interpreting claims founded on anecdotes and for evaluating the clinical studies of marijuana presented in chapter 4.

The Value of Animal Studies

Much of the research into the effects of cannabinoids on the brain is based on animal studies. Many speakers at the public workshops associated with this study argued that animal studies of marijuana are not relevant to humans. Animal studies are not a substitute for clinical trials, but they are a necessary complement. Ultimately, every biologically active substance exerts its effects at the cellular and molecular levels, and the evidence has shown that this is remarkably consistent among mammals, even those as different in body and mind as rats and humans. Animal studies typically provide information about how drugs work that would not be obtainable in clinical studies. At the same time, animal studies can never inform us completely about the full range of psychological and physiological effects of marijuana or cannabinoids on humans.

The Active Constituents of Marijuana

Δ^9 -THC and Δ^8 -THC are the only compounds in the marijuana plant that produce all the psychoactive effects of marijuana. Because Δ^9 -THC is much more abundant than Δ^8 -THC, the psychoactivity of marijuana has been attributed largely to the effects of Δ^9 -THC. 11-OH- Δ^9 -THC is the primary product of Δ^9 -THC metabolism by the liver and is about three times as potent as Δ^9 -THC.¹²⁸

There have been considerably fewer experiments with cannabinoids other than Δ^9 -THC, although a few studies have been done to examine whether other cannabinoids modulate the effects of THC or mediate the nonpsychological effects of marijuana. Cannabidiol (CBD) does not have the same psychoactivity as THC, but it was initially reported to attenuate the psychological response to THC in humans;^{81,177} however, later studies reported that CBD did not attenuate the psychological effects of THC.^{11,69} One double-blind study of eight volunteers reported that CBD can block the anxiety induced by high doses of THC (0.5 mg/kg).¹⁷⁷ There are numerous anecdotal reports claiming that marijuana with relatively higher ratios of THC:CBD is less likely to induce anxiety in the user than marijuana with low THC:CBD ratios; but, taken together, the results published thus far are inconclusive.

The most important effect of CBD seems to be its interference with drug metabolism, including Δ^9 -THC metabolism in the liver.^{14,114} It exerts that effect by inactivating cytochrome P450s, which are the most important class of enzymes that metabolize drugs. Like many P450 inactivators, CBD can also induce P450s after repeated doses.¹³ Experiments in which mice were treated with CBD followed by THC showed that CBD treatment was associated with a substantial increase in brain concentrations of

THC and its major metabolites, most likely because it decreased the rate of clearance of THC from the body.¹⁵

In mice, THC inhibits the release of luteinizing hormone, the pituitary hormone that triggers the release of testosterone from the testes; this effect is increased when THC is given with cannabiniol or CBD.¹¹³

Cannabiniol also lowers body temperature and increases sleep duration in mice.¹⁷⁵ It is considerably less active than THC in the brain, but studies of immune cells have shown that it can modulate immune function (see “Cannabinoids and the Immune System” later in this chapter).

The Pharmacological Toolbox

A researcher needs certain key tools in order to understand how a drug acts on the brain. To appreciate the importance of these tools, one must first understand some basic principles of drug action. All recent studies have indicated that the behavioral effects of THC are receptor mediated.²⁷ Neurons in the brain are activated when a compound binds to its receptor, which is a protein typically located on the cell surface. Thus, THC will exert its effects only after binding to its receptor. In general, a given receptor will accept only particular classes of compounds and will be unaffected by other compounds.

Compounds that activate receptors are called *agonists*. Binding to a receptor triggers an event or a series of events in the cell that results in a change in the cell’s activity, its gene regulation, or the signals that it sends to neighboring cells (Figure 2.1). This agonist-induced process is called signal transduction.

Another set of tools for drug research, which became available only recently for cannabinoid research, are the *receptor antagonists*, so-called because they selectively bind to a receptor that would have otherwise been available for binding to some other compound or drug. Antagonists block the effects of agonists and are tools to identify the functions of a receptor by showing what happens when its normal functions are blocked. Agonists and antagonists are both *ligands*; that is, they bind to receptors. Hormones, neurotransmitters, and drugs can all act as ligands. Morphine and naloxone provide a good example of how agonists and antagonists interact. A large dose of morphine acts as an agonist at opioid receptors in the brain and interferes with, or even arrests, breathing. Naloxone, a powerful opioid antagonist, blocks morphine’s effects on opiate receptors, thereby allowing an overdose victim to resume breathing normally. Naloxone itself has no effect on breathing.

Another key tool involves identifying the receptor protein and determining how it works. That makes it possible to locate where a drug activates its receptor in the brain—both the general region of the brain and

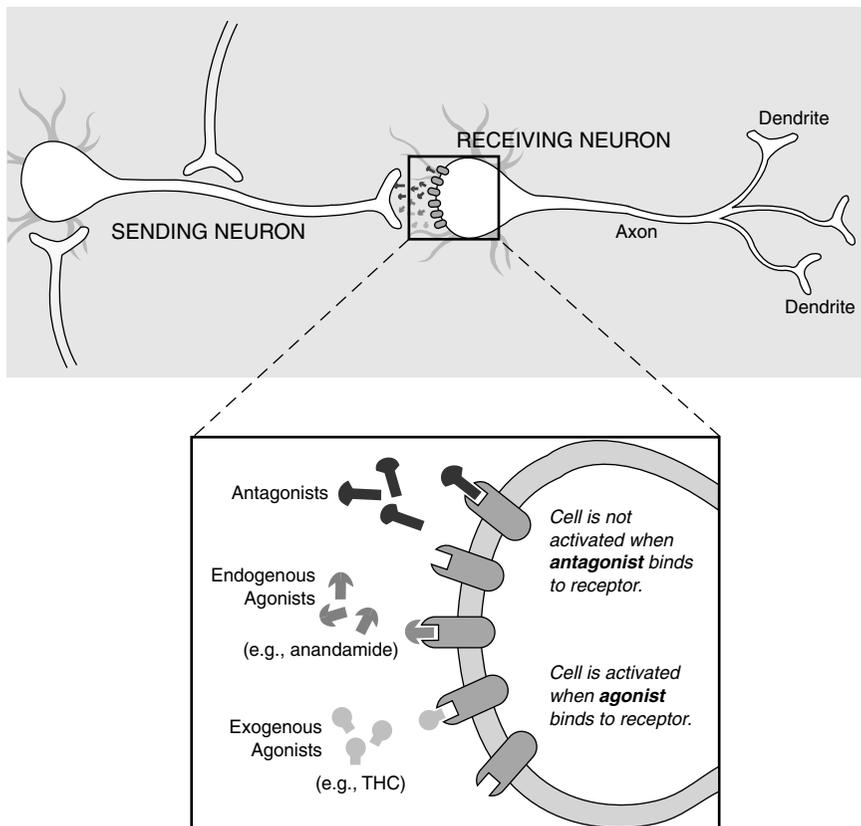


FIGURE 2.1 Diagram of neuron with synapse. Individual nerve cells, or neurons, both send and receive cellular signals to and from neighboring neurons, but for the purposes of this diagram only one activity is indicated for each cell. Neurotransmitter molecules are released from the neuron terminal and move across the gap between the “sending” and “receiving” neurons. A signal is transmitted to the receiving neuron when the neurotransmitters have bound to the receptor on its surface. The effects of a transmitted signal include:

- Changing the cell’s permeability to ions, such as calcium and potassium.
- Turning a particular gene on or off.
- Sending a signal to another neuron.
- Increasing or decreasing the responsiveness of the cell to other cellular signals.

Those effects can lead to cognitive, behavioral, or physiological changes, depending on which neuronal system is activated.

Continued on bottom of p. 39

the cell type where the receptor is located. The way to find a receptor for a drug in the brain is to make the receptor “visible” by attaching a radioactive or fluorescent marker to the drug. Such markers show where in the brain a drug binds to the receptor, although this is not necessarily the part of the brain where the drug ultimately has its greatest effects.

Because drugs injected into animals must be dissolved in a water-based solution, it is easier to deliver water-soluble molecules than to deliver fat-soluble (lipophilic) molecules such as THC. THC is so lipophilic that it can stick to glass and plastic syringes used for injection. Because it is lipophilic, it readily enters cell membranes and thus can cross the blood brain barrier easily. (This barrier insulates the brain from many blood-borne substances.) Early cannabinoid research was hindered by the lack of potent cannabinoid ligands (THC binds to its cannabinoid receptors rather weakly) and because they were not readily water soluble. The synthetic agonist CP 55,940, which is more water soluble than THC, was the first useful research tool for studying cannabinoid receptors because of its high potency and ability to be labeled with a radioactive molecule, which enabled researchers to trace its activity.

CANNABINOID RECEPTORS

The cannabinoid receptor is a typical member of the largest known family of receptors: the G protein-coupled receptors with their distinctive pattern in which the receptor molecule spans the cell membrane seven times (Figure 2.2). For excellent recent reviews of cannabinoid receptor biology, see Childers and Breivogel,²⁷ Abood and Martin,¹ Felder and Glass,⁴³ and Pertwee.¹²⁴ Cannabinoid receptor ligands bind *reversibly* (they bind to the receptor briefly and then dissociate) and *stereoselectively* (when there are molecules that are mirror images of each other, only one

The expanded view of the synapse illustrates a variety of *ligands*, that is, molecules that bind to receptors. Anandamide is a substance produced by the body that binds to and activates cannabinoid receptors; it is an *endogenous agonist*. THC can also bind to and activate cannabinoid receptors but is not naturally found in the body; it is an *exogenous agonist*. SR 141716A binds to but does not activate cannabinoid receptors. In this way it prevents agonists, such as anandamide and THC, from activating cannabinoid receptors by binding to the receptors without activating them; SR 141716A is an *antagonist*, but it is not normally produced in the body. Endogenous antagonists, that is, those normally produced in the body, might also exist, but none has been identified.

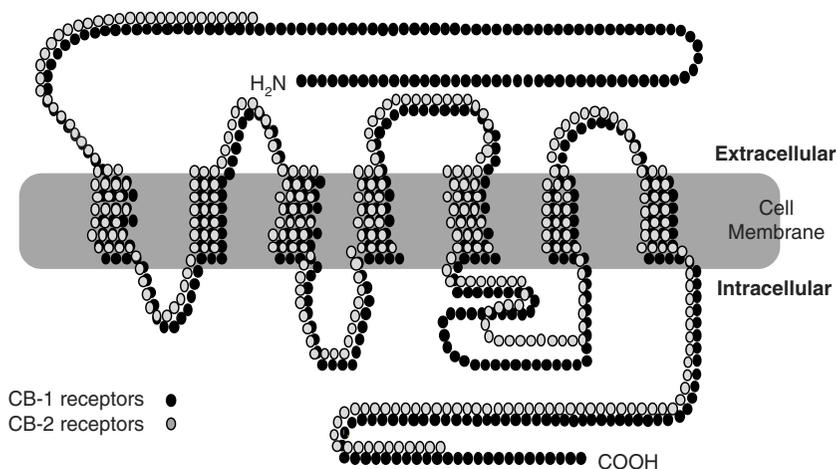


FIGURE 2.2 Cannabinoid receptors. Receptors are proteins, and proteins are made up of strings of amino acids. Each circle in the diagram represents one amino acid. The shaded bar represents the cell membrane, which like all cell membranes in animals is composed largely of phospholipids. Like many receptors, the cannabinoid receptors span the cell membrane; some sections of the receptor protein are outside the cell membrane (extracellular); some are inside (intracellular). THC, anandamide, and other known cannabinoid receptor agonists bind to the extracellular portion of the receptor, thereby activating the signal pathway inside the cell. The CB₁ molecule is larger than CB₂. The receptor molecules are most similar in four of the seven regions where they are embedded in the cell membrane (known as the transmembrane regions). The intracellular loops of the two receptor subtypes are quite different, which might affect the cellular response to the ligand because these loops are known to mediate G protein signaling, the next step in the cell signaling pathway after the receptor. Receptor homology between the two receptor subtypes is 44% for the full-length protein and 68% within the seven transmembrane regions. The ligand binding sites are typically defined by the extracellular loops and the transmembrane regions.

version activates the receptor). Thus far, two cannabinoid receptor subtypes (CB₁ and CB₂) have been identified, of which only CB₁ is found in the brain.

The cell responds in a variety of ways when a ligand binds to the cannabinoid receptor (Figure 2.3). The first step is activation of G proteins, the first components of the signal transduction pathway. That leads to changes in several intracellular components—such as cyclic AMP and calcium and potassium ions—which ultimately produce the changes in cell functions. The final result of cannabinoid receptor stimulation de-

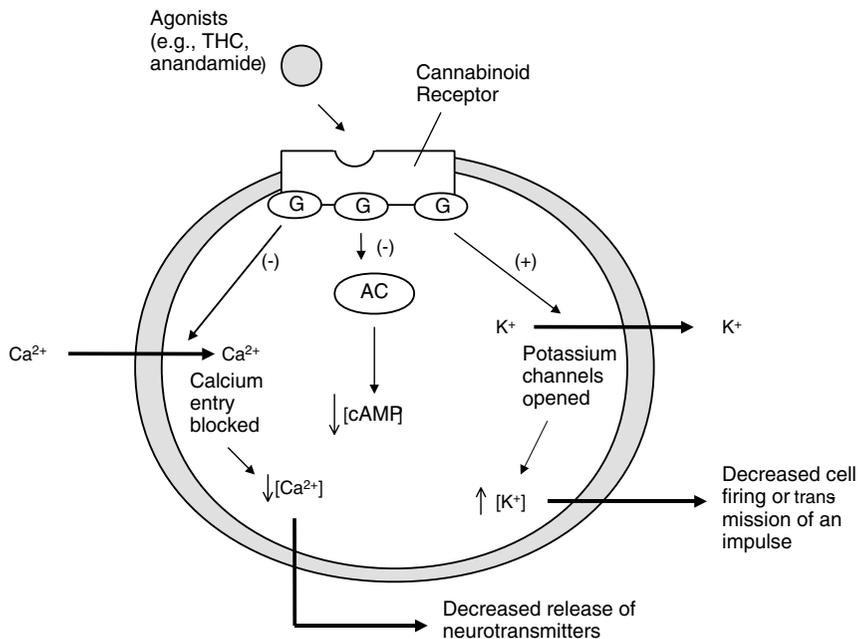


FIGURE 2.3 Cannabinoid agonists trigger a series of reactions within cells. Cannabinoid receptors are embedded in the cell membrane, where they are coupled to G proteins (G) and the enzyme adenylyl cyclase (AC). Receptors are activated when they bind to ligands, such as anandamide or THC in this case. This triggers a variety of reactions, including inhibition (-) of AC, which decreases the production of cAMP and cellular activities dependent on cAMP; opening of potassium (K^+) channels, which decreases cell firing; and closing of calcium (Ca^{2+}) channels, which decreases the release of neurotransmitters. Each of those changes can influence cellular communication.

depends on the particular type of cell, the particular ligand, and the other molecules that might be competing for receptor binding sites. Different agonists vary in binding *potency*, which determines the effective dose of the drug, and *efficacy*, which determines the maximal strength of the signal that they transmit to the cell. The potency and efficacy of THC are both relatively lower than those of some synthetic cannabinoids; in fact, synthetic compounds are generally more potent and efficacious than endogenous agonists.

CB_1 receptors are extraordinarily abundant in the brain. They are more abundant than most other G protein-coupled receptors and 10 times more abundant than *mu* opioid receptors, the receptors responsible for the effects of morphine.¹⁴⁸

The cannabinoid receptor in the brain is a protein referred to as CB₁. The peripheral receptor (outside the nervous system), CB₂, is most abundant on cells of the immune system and is not generally found in the brain.^{43,124} Although no other receptor subtypes have been identified, there is a genetic variant known as CB₁A (such variants are somewhat different proteins that have been produced by the same genes via alternative processing). In some cases, proteins produced via alternative splicing have different effects on cells. It is not yet known whether there are any functional differences between the two, but the structural differences raise the possibility.

CB₁ and CB₂ are similar, but not as similar as members of many other receptor families are to each other. On the basis of a comparison of the sequence of amino acids that make up the receptor protein, the similarity of the CB₁ and CB₂ receptors is 44% (Figure 2.2). The differences between the two receptors indicate that it should be possible to design therapeutic drugs that would act only on one or the other receptor and thus would activate or attenuate (block) the appropriate cannabinoid receptors. This offers a powerful method for producing biologically selective effects. In spite of the difference between the receptor subtypes, most cannabinoid compounds bind with similar affinity* to both CB₁ and CB₂ receptors. One exception is the plant-derived compound CBD, which appears to have greater binding affinity for CB₂ than for CB₁,¹¹² although another research group has failed to substantiate that observation.¹²⁹ Other exceptions include the synthetic compound WIN 55,212-2, which shows greater affinity for CB₂ than CB₁, and the endogenous ligands, anandamide and 2-AG, which show greater affinity for CB₁ than CB₂.⁴³ The search for compounds that bind to only one or the other of the cannabinoid receptor types has been under way for several years and has yielded a number of compounds that are useful research tools and have potential for medical use.

Cannabinoid receptors have been studied most in vertebrates, such as rats and mice. However, they are also found in invertebrates, such as leeches and mollusks.¹⁵⁶ The evolutionary history of vertebrates and invertebrates diverged more than 500 million years ago, so cannabinoid receptors appear to have been conserved throughout evolution at least this long. This suggests that they serve an important and basic function in animal physiology. In general, cannabinoid receptor molecules are similar among different species.¹²⁴ Thus, cannabinoid receptors likely fill many similar functions in a broad range of animals, including humans.

**Affinity* is a measure of how avidly a compound binds to a receptor. The higher the affinity of a compound, the higher its potency; that is, lower doses are needed to produce its effects.

THE ENDOGENOUS CANNABINOID SYSTEM

For any drug for which there is a receptor, the logical question is, "Why does this receptor exist?" The short answer is that there is probably an endogenous agonist (that is, a compound that is naturally produced in the brain) that acts on that receptor. The long answer begins with a search for such compounds in the area of the body that produces the receptors and ends with a determination of the natural function of those compounds. So far, the search has yielded several endogenous compounds that bind selectively to cannabinoid receptors. The best studied of them are anandamide³⁷ and arachidonyl glycerol (2-AG).¹⁰⁸ However, their physiological roles are not yet known.

Initially, the search for an endogenous cannabinoid was based on the premise that its chemical structure would be similar to that of THC; that was reasonable, in that it was really a search for another "key" that would fit into the cannabinoid receptor "keyhole," thereby activating the cellular message system. One of the intriguing discoveries in cannabinoid biology was how chemically different THC and anandamide are. A similar search for endogenous opioids (endorphins) also revealed that their chemical structure is very different from the plant-derived opioids, opium and morphine.

Further research has uncovered a variety of compounds with quite different chemical structures that can activate cannabinoid receptors (Table 2.2 and Figure 2.4). It is not yet known exactly how anandamide and THC bind to cannabinoid receptors. Knowing this should permit more precise design of drugs that selectively activate the endogenous cannabinoid systems.

Anandamide

The first endogenous cannabinoid to be discovered was arachidonyl-ethanolamine, named anandamide from the Sanskrit word *ananda*, meaning "bliss."³⁷ Compared with THC, anandamide has only moderate affinity for CB₁ receptor and is rapidly metabolized by amidases (enzymes that remove amide groups). Despite its short duration of action, anandamide shares most of the pharmacological effects of THC.^{37,152} Rapid degradation of active molecules is a feature of neurotransmitter systems that allows them control of signal timing by regulating the abundance of signaling molecules. It creates problems for interpreting the results of many experiments and might explain why *in vivo* studies with anandamide injected into the brain have yielded conflicting results.

Anandamide appears to have both central (in the brain) and peripheral (in the rest of the body) effects. The precise neuroanatomical localiza-

TABLE 2.2 Compounds That Bind to Cannabinoid Receptors

Compound	Properties
Agonists (receptor activators)	
<i>Plant-derived compounds</i>	
Δ^9 -THC	Main psychoactive cannabinoid in marijuana plant; largely responsible for psychological and physiological effects (except in discussions of the different forms of THC, THC is used as a synonym for Δ^9 -THC).
Δ^8 -THC	Slightly less potent than Δ^9 -THC and much less abundant in marijuana plant but otherwise similar.
11-OH- Δ^9 -THC	Bioactive compound formed when body breaks down Δ^9 -THC; presumed to be responsible for some effects of marijuana.
<i>Cannabinoid agonists found in animals</i>	
Anandamide (arachidonyl-ethanolamide)	Found in animals ranging from mollusks to mammals; appears to be primary endogenous cannabinoid agonist in mammals; chemical structure very different from plant cannabinoids and related to prostaglandins.
2-AG (arachidonyl glycerol)	Endogenous agonist; structurally similar to anandamide; more abundant but less potent than anandamide.
<i>THC analogues</i>	
Dronabinol	Synthetic THC; marketed in the United States as Marinol for nausea associated with chemotherapy and for AIDS-related wasting.
Nabilone	THC analogue; marketed in the United Kingdom as Cesamet for same indications as dronabinol.
CP 55,940	Synthetic cannabinoid; THC analogue; that is, it is structurally similar to THC.
Levonantradol	THC analogue.
HU-210	THC analogue, 100- to 800-fold greater potency than THC ⁹⁷ .
<i>Chemical structure unlike THC or anandamide</i>	
WIN-55,212-2	Chemical structure different from known cannabinoids, but binds to both cannabinoid receptors; chemically related to cyclo-oxygenase inhibitors, which include antiinflammatory drugs.
Antagonists (receptor blockers)	
SR 141716A	Synthetic CB ₁ antagonist; developed in 1994 ¹³² .
SR 144528	Synthetic CB ₂ antagonist; developed in 1997 ¹³³ .

SOURCES: Mechoulam et al., 1998;¹⁰⁹ Felder and Glass, 1998;⁴³ and British Medical Association.¹⁷

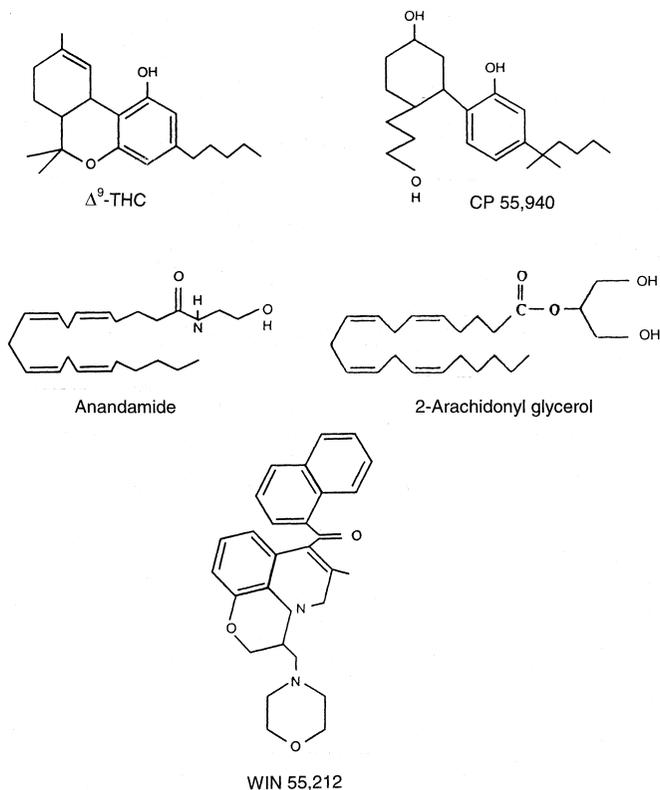


FIGURE 2.4 Chemical structures of selected cannabinoid agonists or molecules that bind to and activate cannabinoid receptors. **THC** is the primary psychoactive molecule found in marijuana. **CP 55,940** is a THC analogue; that is, its chemical structure is related to THC. **Anandamide** and **2-arachidonyl glycerol (2-AG)** are endogenous molecules, meaning they are naturally produced in the body. Although the chemical structure of **WIN 55,212** is very different from either THC or anandamide, it is also a cannabinoid agonist.

tion of anandamide and the enzymes that synthesize it are not yet known. This information will provide essential clues to the natural role of anandamide and an understanding of the brain circuits in which it is a neurotransmitter. The importance of knowing specific brain circuits that involve anandamide (and other endogenous cannabinoid ligands) is that such circuits are the pivotal elements for regulating specific brain functions, such as mood, memory, and cognition. Anandamide has been found in numerous regions of the human brain: hippocampus (and

TABLE 2.3 Comparison of Cannabinoid Receptor Agonists

Potency can be measured in a variety of ways, from behavioral to physiological to cellular. This table shows potency in terms of receptor binding, which is the most broadly applicable to the many possible actions of cannabinoids. For example, anandamide binds to the cannabinoid receptor only about half as avidly as does THC. Measures of potency might include effects on activity (behavior) or hypothermia (physiologic).

The apparently low potency of 2-AG may, however, be misleading. A study published late in 1998 reports that 2-AG is found with two other closely related compounds that by themselves are biologically inactive; but in the presence of those two compounds, 2-AG is only three times less active than THC.⁹ Further, 2-AG is much more abundant than anandamide, although the biological significance of this remains to be determined.

Receptor Binding in Brain Tissue¹²⁴

Compound	Potency Relative to Δ^9 -THC
CP 55,940	59
Δ^9 -THC	1
Anandamide	0.47
2-AG	0.08

parahippocampic cortex), striatum, and cerebellum; but it has not been precisely identified with specific neuronal circuits. CB₁ receptors are abundant in these regions, and this further implies a physiological role for endogenous cannabinoids in the brain functions controlled by these areas. But substantial concentrations of anandamide are also found in the thalamus, an area of the brain that has relatively few CB₁ receptors.¹²⁴

Anandamide has also been found outside the brain. It has been found in spleen tissue, which also has high concentrations of CB₂ receptors, and small amounts have been detected in heart tissue.⁴⁴

In general, the affinity of anandamide for cannabinoid receptors is only one-fourth to one-half that of THC (see Table 2.3). The differences depend on the cells or tissue that are tested and on the experimental conditions, such as the binding assay used (reviewed by Pertwee¹²⁴).

The molecular structure of anandamide is relatively simple, and it can be formed from arachidonic acid and ethanolamine. Arachidonic acid is a common precursor of a group of biologically active molecules known as eicosanoids, including prostaglandins.* Although anandamide can be synthesized in a variety of ways, the physiologically relevant pathway

*Eicosanoids all contain a chain of 20 carbon atoms and are named after *eikosi*, the Greek word for 20.

seems to be through enzymatic cleavage of *N*-arachidonyl-phosphatidylethanolamine (NAPE), which yields anandamide and phosphatidic acid (reviewed by Childers and Breivogel²⁷).

Anandamide can be inactivated in the brain via two mechanisms. In one it is enzymatically cleaved to yield arachidonic acid and ethanolamine—the reverse of what was initially proposed as its primary mode of synthesis. In the other it is inactivated through neuronal uptake—that is, by being transported into the neuron, which prevents its continuing activation of neighboring neurons.

Other Endogenous Agonists

Several other endogenous compounds that are chemically related to anandamide and that bind to cannabinoid receptors have been discovered, one of which is 2-AG.¹⁰⁸ 2-AG is closely related to anandamide and is even more abundant in the brain. At the time of this writing, all known endogenous cannabinoid receptor agonists (including anandamide) were eicosanoids, which are arachidonic acid metabolites. Arachidonic acid (a free fatty acid) is released via hydrolysis of membrane phospholipids.

Other, noneicosanoid, compounds that bind cannabinoid receptors have recently been isolated from brain tissue, but they have not been identified, and their biological effects are under investigation. This is a fast-moving field of research, and no review over six months old will be fully up to date.

The endogenous compounds that bind to cannabinoid receptors probably perform a broad range of natural functions in the brain. This neural signaling system is rich and complex and has many subtle variations, many of which await discovery. In the next few years much more will probably be known about these naturally occurring cannabinoids.

Some effects of cannabinoid agonists are receptor independent. For example, both THC and CBD can be neuroprotective through their antioxidative activity; that is, they can reduce the toxic forms of oxygen that are released when cells are under stress.⁵⁴ Other likely examples of receptor-independent cannabinoid activity are modulation of activation of membrane-bound enzymes (such as ATPase), arachidonic acid release, and perturbation of membrane lipids. An important caution in interpreting those reports is that concentrations of THC or CBD used in cellular studies, such as these, are generally much higher than the concentrations of THC or CBD in the body that would likely be achieved by smoking marijuana.

TABLE 2.4 Cellular Processes That Can Be Targeted for Drug Development

Drug Action		Biological Result
Block synthesis	Synthesis of bioactive compounds is a continuous process and is one means by which concentrations of that compound are regulated.	<i>Weaker signal</i> , due to decreased agonist concentration.
Inhibit degradation	Chemical breakdown is one method the body uses to inactivate endogenous substances.	<i>Stronger signal</i> , due to increased agonist concentration.
Facilitate neuronal uptake	Neuronal uptake is one of the natural ways in which a receptor agonist is inactivated.	<i>Stronger signal</i> , due to increased amount of time during which agonist is present in the synapse where it can stimulate the receptor.

NOTE: Endogenous cannabinoids are part of a cellular signaling system. This table lists categories of natural processes that regulate such systems and shows the results of altering those processes.

Novel Targets for Therapeutic Drugs

Drugs that alter the natural biology of anandamide or other endogenous cannabinoids might have therapeutic uses (Table 2.4). For example, drugs that selectively inhibit neuronal uptake of anandamide would increase the brain's own natural cannabinoids, thereby mimicking some of the effects of THC. A number of important psychotherapeutic drugs act by inhibiting neurotransmitter uptake. For example, antidepressants like fluoxetine (Prozac) inhibit serotonin uptake and are known as selective serotonin reuptake inhibitors, or SSRIs. Another way to alter levels of endogenous cannabinoids would be to develop drugs that act on the enzymes involved in anandamide synthesis. Some antihypertensive drugs work by inhibiting enzymes involved in the synthesis of endogenous hypertensive agents. For example, anti-converting enzyme (ACE) inhibitors are used in hypertensive patients to interfere with the conversion of angiotensin I, which is inactive, to the active hormone, angiotensin II.

SITES OF ACTION

Cannabinoid receptors are particularly abundant in some areas of the brain. The normal biology and behavior associated with these brain areas

TABLE 2.5 Brain Regions in Which Cannabinoid Receptors Are Abundant

Brain Region	Functions Associated with Region
Brain regions in which cannabinoid receptors are abundant	
Basal ganglia	Movement control
Substantia nigra pars reticulata	
Entopeduncular nucleus	
Globus pallidus	
Putamen	
Cerebellum	Body movement coordination
Hippocampus	Learning and memory, stress
Cerebral cortex, especially cingulate, frontal, and parietal regions	Higher cognitive functions
Nucleus accumbens	Reward center
Brain regions in which cannabinoid brain receptors are moderately concentrated	
Hypothalamus	Body housekeeping functions (body temperature regulation, salt and water balance, reproductive function)
Amygdala	Emotional response, fear
Spinal cord	Peripheral sensation, including pain
Brain stem	Sleep and arousal, temperature regulation, motor control
Central gray	Analgesia
Nucleus of the solitary tract	Visceral sensation, nausea and vomiting

SOURCES: Based on reviews by Pertwee (1997b)¹²⁴ and Herkenham (1995).⁵⁷

are consistent with the behavioral effects produced by cannabinoids (Table 2.5 and Figure 2.5). The highest receptor density is found in cells of the basal ganglia that project locally and to other brain regions. These cells include the substantia nigra pars reticulata, entopeduncular nucleus, and globus pallidus, regions that are generally involved in coordinating body movements. Patients with Parkinson's or Huntington's disease tend to have impaired functions in these regions.

CB₁ receptors are also abundant in the putamen, part of the relay system within the basal ganglia that regulates body movements; the cerebellum, which coordinates body movements; the hippocampus, which is involved in learning, memory, and response to stress; and the cerebral cortex, which is concerned with the integration of higher cognitive functions.

CB₁ receptors are found on various parts of neurons, including the

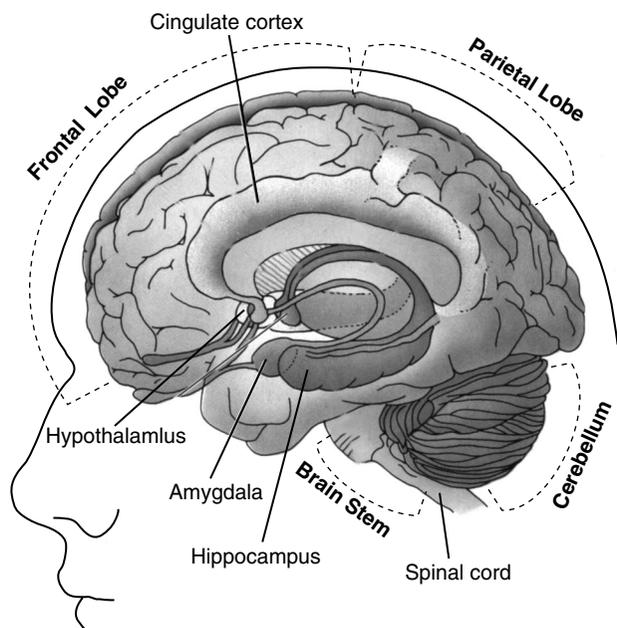


FIGURE 2.5 Locations of brain regions in which cannabinoid receptors are abundant. See Table 2.5 for a summary of functions associated with those regions.

axon, cell bodies, terminals, and dendrites.^{57,165} Dendrites are generally the “receiving” part of a neuron, and receptors on axons or cell bodies generally modulate other signals. Axon terminals are the “sending” part of the neuron.

Cannabinoids tend to inhibit neurotransmission, although the results are somewhat variable. In some cases, cannabinoids diminish the effects of the inhibitory neurotransmitter, *g*-aminobutyric acid (GABA);¹⁴⁴ in other cases, cannabinoids can augment the effects of GABA.¹²⁰ The effect of activating a receptor depends on where it is found on the neuron: if cannabinoid receptors are presynaptic (on the “sending” side of the synapse) and inhibit the release of GABA, cannabinoids would diminish GABA effects; the net effect would be stimulation. However, if cannabinoid receptors are postsynaptic (on the “receiving” side of the synapse) and on the same cell as GABA receptors, they will probably mimic the effects of GABA; in that case, the net effect would be inhibition.^{120,144,160}

CB₁ is the predominant brain cannabinoid receptor. CB₂ receptors have not generally been found in the brain, but there is one isolated report suggesting some in mouse cerebellum.¹⁵⁰ CB₂ is found primarily on cells

TABLE 2.6 Cannabinoid Receptors

	CB ₁	CB ₂
Effects of various cannabinoids		
Δ ⁹ -THC	Agonist	Weak antagonist
Anandamide	Agonist	Agonist
Cannabinol	Weak agonist	Agonist; greater affinity for CB ₂ than for CB ₁
Cannabidiol	Does not bind to receptor	Does not bind to receptor
Receptor distribution		
Areas of greatest abundance	Brain	Immune system, especially B cells and natural killer cells

of the immune system. CB₁ receptors are also found in immune cells, but CB₂ is considerably more abundant there (Table 2.6) (reviewed by Kaminski⁸⁰ in 1998).

As can be appreciated in the next section, the presence of cannabinoid systems in key brain regions is strongly tied to the functions and pathology associated with those regions. The clinical value of cannabinoid systems is best understood in the context of the biology of these brain regions.

CANNABINOID RECEPTORS AND BRAIN FUNCTIONS

Motor Effects

Marijuana affects psychomotor performance in humans. The effects depend both on the nature of the task and the experience with marijuana. In general, effects are clearest in steadiness (body sway and hand steadiness) and in motor tasks that require attention. The results of testing cannabinoids in rodents are much clearer.

Cannabinoids clearly affect movement in rodents, but the effects depend on the dose: low doses stimulate and higher doses inhibit locomotion.^{111,159} Cannabinoids mainly inhibit the transmission of neural signals, and they inhibit movement through their actions on the basal ganglia and cerebellum, where cannabinoid receptors are particularly abundant (Figure 2.6). Cannabinoid receptors are also found in the neurons that project from the striatum and subthalamic nucleus, which inhibit and stimulate movement, respectively.^{58,101}

Cannabinoids decrease both the inhibitory and stimulatory inputs to the substantia nigra and therefore might provide dual regulation of move-

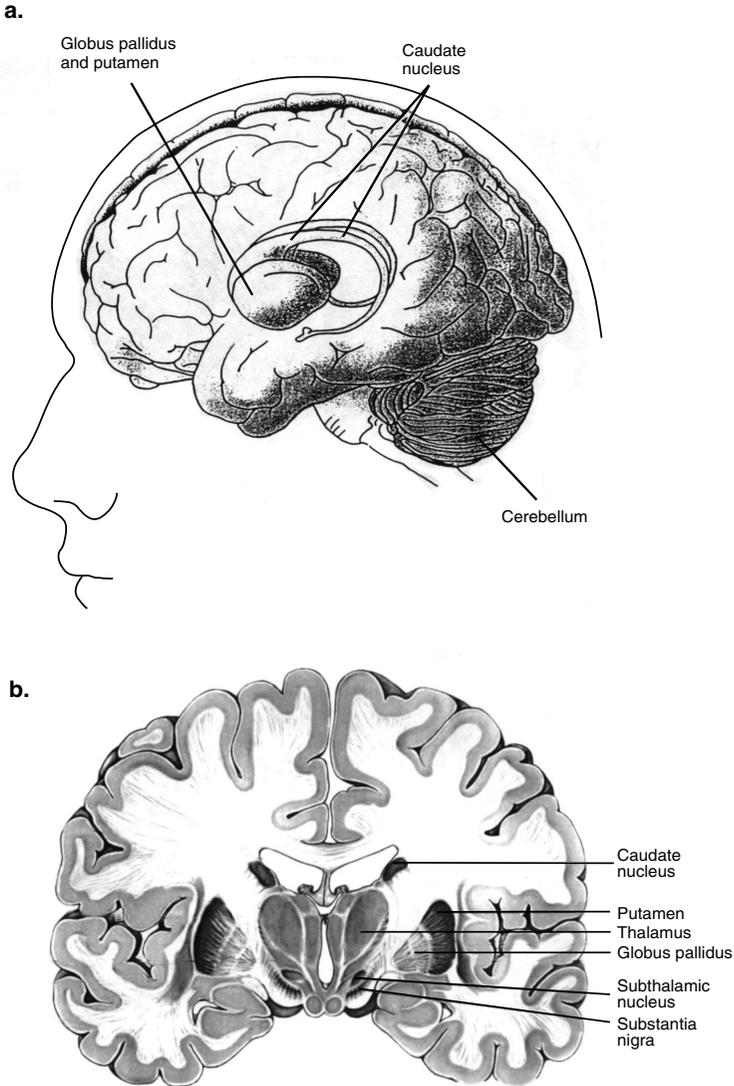


FIGURE 2.6 Diagrams showing motor regions of the brain. Basal ganglia are a group of three brain regions, or nuclei—**caudate**, **putamen**, and **globus pallidus**. Figure 2.6a is a three-dimensional view showing the location of those nuclei in the brain. Figure 2.6b shows those structures in a vertical cross-sectional view. The major output pathways of the basal ganglia arise from the globus pallidus and pars reticulata of the **substantia nigra**. Their main target is the **thalamus**. SOURCE: Figure 2.6a is reprinted from *Principles of Neural Science*, 2nd ed., 1985 (E.R. Kandel and J.H. Schwartz, eds.), with permission from the copyright holder, Appleton and Lange.

ment at this nucleus. In the substantia nigra, cannabinoids decrease transmission from both the striatum and the subthalamic nucleus.¹⁴¹ The globus pallidus has been implicated in mediating the cataleptic effects of large doses of cannabinoids in rats.¹²⁶ (Catalepsy is a condition of diminished responsiveness usually characterized by trancelike states and waxy rigidity of the muscles.) Several other brain regions—the cortex, the cerebellum, and the neural pathway from cortex to striatum—are also involved in the control of movement and contain abundant cannabinoid receptors.^{52,59,101} They are therefore possible additional sites that might underlie the effects of cannabinoids on movement.

Memory Effects

One of the primary effects of marijuana in humans is disruption of short-term memory.⁶⁸ That is consistent with the abundance of CB₁ receptors in the hippocampus, the brain region most closely associated with memory. The effects of THC resemble a temporary hippocampal lesion.⁶³ Deadwyler and colleagues have demonstrated that cannabinoids decrease neuronal activity in the hippocampus and its inputs.^{23,24, 83} *In vitro*, several cannabinoid ligands and endogenous cannabinoids can block the cellular processes associated with memory formation.^{29,30,116,157,163} Furthermore, cannabinoid agonists inhibit release of several neurotransmitters: acetylcholine from the hippocampus,⁴⁹⁻⁵¹ norepinephrine from human and guinea pig (but not rat or mouse) hippocampal slices,¹⁴³ and glutamate in cultured hippocampal cells.¹⁴⁴ Cholinergic and noradrenergic neurons project into the hippocampus, but circuits within the hippocampus are glutamatergic.* Thus, cannabinoids could block transmission both into and within the hippocampus by blocking presynaptic neurotransmitter release.

Pain

After nausea and vomiting, chronic pain was the condition cited most often to the IOM study team as a medical use for marijuana. Recent research presented below has shown intriguing parallels with anecdotal reports of the modulating effects of cannabinoids on pain—both the effects of cannabinoids acting alone and the effects of their interaction with opioids.

*Neurons are often defined by the primary neurotransmitter released at their terminals. Thus, *cholinergic* neurons release acetylcholine, *noradrenergic* neurons release noradrenalin (also known as norepinephrine), and *glutamergic* neurons release glutamate.

Behavioral Studies

Cannabinoids reduce reactivity to acute painful stimuli in laboratory animals. In rodents, cannabinoids reduced the responsiveness to pain induced through various stimuli, including thermal, mechanical, and chemical stimuli.^{12,19,46,72,96,154,174} Cannabinoids were comparable with opiates in potency and efficacy in these experiments.^{12,72}

Cannabinoids are also effective in rodent models of chronic pain. Herzberg and co-workers found that cannabinoids can block allodynia and hyperalgesia associated with neuropathic pain in rats.⁶² This is an important advance because chronic pain frequently results in a series of neural changes that increase suffering due to allodynia (pain elicited by stimuli that are normally innocuous), hyperalgesia (abnormally increased reactivity to pain), and spontaneous pain; furthermore, some chronic pain syndromes are not amenable to therapy, even with the most powerful narcotic analgesics.¹⁰

Pain perception is controlled mainly by neurotransmitter systems within the central nervous system, and cannabinoids clearly play a role in the control of pain in those systems.⁴⁵ However, pain-relieving and pain-preventing mechanisms also occur in peripheral tissues, and endogenous cannabinoids appear to play a role in peripheral tissues. Thus, the different cannabinoid receptor subtypes might act synergistically. Experiments in which pain is induced by injecting dilute formalin into a mouse's paw have shown that anandamide and palmitylethanolamide (PEA) can block peripheral pain.^{22,73} Anandamide acts primarily at the CB₁ receptor, whereas PEA has been proposed as a possible CB₂ agonist; in short, there might be a biochemical basis for their independent effects. When injected together, the analgesic effect is stronger than that of either alone. That suggests an important strategy for the development of a new class of analgesic drug: a mixture of CB₁ and CB₂ agonists. Because there are few, if any, CB₂ receptors in the brain, it might be possible to develop drugs that enhance the peripheral analgesic effect while minimizing the psychological effects.

Neural Sites of Altered Responsiveness to Painful Stimuli

The brain and spinal cord mediate cannabinoid analgesia. A number of brain areas participate in cannabinoid analgesia and support the role of descending pathways (neural pathways that project from the brain to the spinal cord).^{103,105} Although more work is needed to produce a comprehensive map of the sites of cannabinoid analgesia, it is clear that the effects are limited to particular areas, most of which have an established role in pain.

Specific sites where cannabinoids act to affect pain processing include the periaqueductal gray,¹⁰⁴ rostral ventral medulla,^{105,110} thalamic nucleus submedius,¹⁰² thalamic ventroposterolateral nucleus,¹⁰² dorsal horn of the spinal cord,^{64,65} and peripheral sensory nerves.^{64-66,131} Those nuclei also participate in opiate analgesia. Although similar to opiate analgesia, cannabinoid analgesia is not mediated by opioid receptors; morphine and cannabinoids sometimes act synergistically, and opioid antagonists generally have no effect on cannabinoid-induced analgesia.¹⁷¹ However, a *kappa*-receptor antagonist has been shown to attenuate spinal, but not supraspinal, cannabinoid analgesia.^{153,170,171} (*Kappa* opioid receptors constitute one of the three major types of opioid receptors; the other two types are *mu* and *delta* receptors.)

Neurophysiology and Neurochemistry of Cannabinoid Analgesia

Because of the marked effects of cannabinoids on motor function, behavioral studies in animals alone cannot provide sufficient grounds for the conclusion that cannabinoids depress pain perception. Motor behavior is typically used to measure responses to pain, but this behavior is itself affected by cannabinoids. Thus, experimental results include an unmeasured combination of cannabinoid effects on motor and pain systems. The effects on specific neural systems, however, can be measured at the neurophysiological and neurochemical levels. Cannabinoids decrease the response of immediate-early genes (genes that are activated in the early or immediate stage of response to a broad range of cellular stimuli) to noxious stimuli in the spinal cord, decrease response of pain neurons in the spinal cord, and decrease the responsiveness of pain neurons in the ventral posterolateral nucleus of the thalamus.^{67,102} Those changes are mediated by cannabinoid receptors, are selective for pain neurons, and are unrelated to changes in skin temperature or depth of anesthesia, and they follow the time course of the changes in behavioral responses to painful stimuli but not the time course of motor changes.⁶⁷ On-cells and off-cells in the rostral ventral medulla control pain transmission at the level of the spinal cord, and cannabinoids also modulate their responses in a manner that is very similar to that of morphine.¹¹⁰

Endogenous Cannabinoids Modulate Pain

Endogenous cannabinoids can modulate pain sensitivity through both central and peripheral mechanisms. For example, animal studies have shown that pain sensitivity can be increased when endogenous cannabinoids are blocked from acting at CB₁ receptors.^{22,62,110,130,158} Administration of cannabinoid antagonists in either the spinal cord¹³⁰ or paw²² in-

crease the sensitivity of animals to pain. In addition, there is evidence that cannabinoids act at the site of injury to reduce peripheral inflammation.¹³¹

Current data suggest that the endogenous cannabinoid analgesic system might offer protection against the long-lasting central hyperalgesia and allodynia that sometimes follow skin or nerve injuries.^{130,158} These results raise the possibility that therapeutic interventions that alter the levels of endogenous cannabinoids might be useful for managing pain in humans.

CHRONIC EFFECTS OF THC

Most substances of abuse produce tolerance, physical dependence, and withdrawal symptoms. *Tolerance* is the most common response to repetitive use of a drug and is the condition in which, after repeated exposure to a drug, increasing doses are needed to achieve the same effect. *Physical dependence* develops as a result of a resetting of homeostatic mechanisms in response to repeated drug use. Tolerance, dependence, and withdrawal are not peculiar to drugs of abuse. Many medicines that are not addicting can produce these types of effects; examples of such medications include clonidine, propranolol, and tricyclic antidepressants. The following sections discuss what is known about the biological mechanisms that underlie tolerance, reward, and dependence; clinical studies about those topics are discussed in chapter 3.

Tolerance

Chronic administration of cannabinoids to animals results in tolerance to many of the acute effects of THC, including memory disruption,³⁴ decreased locomotion,^{2,119} hypothermia,^{42,125} neuroendocrine effects,¹³⁴ and analgesia.⁴ Tolerance also develops to the cardiovascular and psychological effects of THC and marijuana in humans (see also discussion in chapter 3).^{55,56,76}

Tolerance to cannabinoids appears to result from both *pharmacokinetic* changes (how the drug is absorbed, distributed, metabolized, and excreted) and *pharmacodynamic* changes (how the drug interacts with target cells). Chronic treatment with the cannabinoid agonist, CP 55,940, increases the activity of the microsomal cytochrome P450 oxidative system,³¹ the system through which drugs are metabolized in the liver; this suggests pharmacokinetic tolerance. Chronic cannabinoid treatment also produces changes in brain cannabinoid receptors and cannabinoid receptor mRNA concentrations—an indication that pharmacodynamic effects are important as well.

Most studies have found that brain cannabinoid receptor concentra-

tions usually decrease after prolonged exposure to agonists,^{42,119,136,138} although some studies have reported increases¹³⁷ or no changes² in receptor binding in brain. Differences among studies could be due to the particular agonist tested, the assay used, the brain region examined, or the treatment time. For example, the THC analogue, levonantradol, produces a greater desensitization of adenylyl cyclase inhibition than does THC in cultured neuroblastoma cells.⁴⁰ This might be explained by differences in efficacy between these two agonists.^{18,147} A time course study revealed differences among brain regions in the rates and magnitudes of receptor down regulation.¹⁶ Those findings suggest that tolerance to different effects of cannabinoids develops at different rates.

Chronic treatment with THC also produces variable effects on cannabinoid-mediated signal transduction systems. It produces substantial desensitization of cannabinoid-activated G proteins in a number of rat brain regions.¹⁴⁷ The time course of this desensitization varies across brain regions.¹⁶

It is difficult to extend the findings of short-term animal studies to human marijuana use. To simulate long-term use, higher doses are used in animal studies than are normally achieved by smoking marijuana. For example, the average human will feel "high" after injection of THC at a level of 0.06 mg/kg,¹¹⁸ compared with the 10–20 mg/kg per day used in many chronic rat studies. At the same time, doses of marijuana needed to observe behavioral changes in rats (usually changes in locomotor behavior) are substantially higher than doses at which people feel "high." The pharmacokinetics of THC distribution in the body are also dramatically different between rats and humans and depend heavily on whether it is inhaled, injected, or swallowed. It is likely that some of the same biochemical adaptations to chronic cannabinoid administration occur in laboratory animals and humans, but the magnitude of the effects in humans might be less than that in animals in proportion to the doses used.

Reward and Dependence

Experimental animals that are given the opportunity to self-administer cannabinoids generally do not choose to do so, which has led to the conclusion that they are not reinforcing and rewarding.³⁸ However, behavioral⁹⁵ and brain stimulation⁹⁴ studies have shown that THC can be rewarding to animals. The behavioral study used a "place preference" test, in which an animal is given repeated doses of a drug in one place, and is then given a choice between a place where it received the drug and a place where it did not. The animals chose the place where they received the THC. These rewarding effects are highly dose dependent. In all models studied, cannabinoids are only rewarding at midrange; doses that are

too low are not rewarding; doses that are too high can be aversive. Mice will self-administer the cannabinoid agonist WIN 55,212-2 but only at low doses.¹⁰⁶ This effect is specifically mediated by CB₁ receptors and indicates that stimulation of those receptors is rewarding to the mice. Antagonism of cannabinoid receptors is also rewarding in rats; in conditioned place preference tests, animals show a preference for the place they receive the cannabinoid antagonist SR 141716A at both low and high doses.¹⁴⁰ Cannabinoids increase dopamine concentrations in the mesolimbic dopamine system of rats, a pathway associated with reinforcement.^{25,39,161} However, the mechanism by which THC increases dopamine concentrations appears to be different from that of other abused drugs⁵¹ (see chapter 3 for further discussion of reinforcement). THC-induced increases in dopamine are due to increases in the firing rate of dopamine cells in the ventral tegmental area by Δ^9 -THC.⁴⁷ However, these increases in firing rate in the ventral tegmental area could not be explained by increases in the firing of the A10 dopamine cell group, where other abused drugs have been shown to act.⁵¹

Physical dependence on cannabinoids has been observed only under experimental conditions of "precipitated withdrawal" in which animals are first treated chronically with cannabinoids and then given the CB₁ antagonist SR 141716A.^{3,166} The addition of the antagonist accentuates any withdrawal effect by competing with the agonist at receptor sites; that is, the antagonist helps to clear agonists off and keep them off receptor sites. This suggests that, under normal cannabis use, the long half-life and slow elimination from the body of THC and the residual bioactivity of its metabolite, 11-OH-THC, can prevent substantial abstinence symptoms. The precipitated withdrawal produced by SR 141716A has some of the characteristics of opiate withdrawal, but it is not affected by opioid antagonists, and it affects motor systems differently. An earlier study with monkeys also suggested that abrupt cessation of chronic THC is associated with withdrawal symptoms.⁸ Monkeys in that study were trained to work for food after which they were given THC on a daily basis; when the investigators stopped administering THC, the animals stopped working for food.

A study in rats indicated that the behavioral cannabinoid withdrawal syndrome is consistent with the consequences of withdrawal from other drugs of abuse in that it correlates with the effects of stimulation of central amygdaloid corticotropin-releasing hormone release.¹³⁵ However, the withdrawal syndrome for cannabinoids and the corresponding increase in corticotropin-releasing hormone are observed only after administration of the CB₁ antagonist SR 141716A to cannabinoid-tolerant animals.^{3,166} The implications of data based on precipitated withdrawal in animals for human cannabinoid abuse have not been established.¹⁶⁶ Furthermore, acute administration of THC also produces increases in corticotropin-

releasing hormone and adrenocorticotropin release; both are stress-related hormones.⁷¹ This set of withdrawal studies may explain the generally aversive effects of cannabinoids in animals and could indicate that the increase in corticotropin-releasing hormone is merely a rebound effect. Thus, cannabinoids appear to be conforming to some of the neurobiological effects of other drugs abused by humans, but the underlying mechanisms of these actions and their value for determining the reinforcement and dependence liability of cannabinoids in humans remain undetermined.

CANNABINOIDS AND THE IMMUNE SYSTEM

The human body protects itself from invaders, such as bacteria and viruses through the elaborate and dynamic network of organs and cells referred to as the immune system. Cannabinoids, especially THC, can modulate the function of immune cells in various ways—in some cases enhancing and in others diminishing the immune response⁸⁵ (summarized in Table 2.7). However, the natural function of cannabinoids in the immune system is not known. Immune cells respond to cannabinoids in a variety of ways, depending on such factors as drug concentration, timing of drug delivery to leukocytes in relation to antigen stimulation, and type of cell function. Although the chronic effects of cannabinoids on the immune system have not been studied, based on acute exposure studies in experimental animals it appears that THC concentrations that modulate immunological responses are higher than those required for psychoactivity.

The CB₂ receptor gene, which is not expressed in the brain, is particularly abundant in immune tissues, with an expression level 10–100 times higher than that of CB₁. In spleen and tonsils the CB₂ mRNA* content is equivalent to that of CB₁ mRNA in the brain.⁴⁸ The rank order, from high to low, of CB₂ mRNA levels in immune cells is B-cells > natural killer cells >> monocytes > polymorphonuclear neutrophil cells > T8 cells > T4 cells. In tonsils the CB₂ receptors appear to be restricted to B-lymphocyte-enriched areas. In contrast, CB₁ receptors are mainly expressed in the central nervous system and, to a lesser extent, in several peripheral tissues such as adrenal gland, heart, lung, prostate, uterus, ovary, testis, bone marrow, thymus, and tonsils.

*After a gene is transcribed, it is often spliced and modified into mRNA, or message RNA. The CB-2 mRNA is the gene "message" that moves from the cell nucleus into the cytoplasm where it will be translated into the receptor protein.

TABLE 2.7 Effects of Cannabinoids on the Immune System

Drug Tested	Cell Types Tested or Type of Animal Experiment	Drug Concentration*
THC, 2-AG, 11-OH-THC, CBN	Lymphocytes and splenocytes <i>in vitro</i>	0.1–30 μM
THC, 2-AG	Lymphocytes and splenocytes	0.1–25 μM
Anandamide	Splenocytes <i>in vitro</i>	1–25 μM
THC, 11-OH-THC, 2-AG	Splenocytes <i>in vitro</i>	3–30 μM
THC, CP 55,940, WIN 55,212-2	Lymphocytes <i>in vitro</i>	0.1–100 nM (0.0001–0.1 μM)
THC	Drug injected into mice	>5 mg/kg
HU-210	Drug injected into mice	>0.05 mg/kg
THC, 11-OH-THC, CBD, CP 55,940, CBN	Splenocytes <i>in vitro</i>	1–30 μM
THC	Drug injected into rodents	3 mg/kg per day for 25 days, 40 mg/kg per day for 2 days
THC, 11-OH-THC	Natural killer cells <i>in vitro</i>	0.1–32 μM
THC	Peritoneal macrophages and monocytes	3–30 μM
THC, CBD	Drug injected into mice; in one case, <i>in vitro</i> tests done on spleens	>5 mg/kg per day for 4 days or 50 mg/kg every 5 days for up to 8 weeks
THC, CBD	Peripheral blood mononuclear cells <i>in vitro</i>	<0.1 μM 30 μM
THC, CBD	Splenocytes and T cells <i>in vitro</i>	10 μM
THC	Phorbol myristate acetate-differentiated macrophage <i>in vitro</i>	10–20 μM
THC	Endotoxin-activated macrophages <i>in vitro</i>	10–30 μM
THC	Peritoneal macrophages <i>in vitro</i>	10–30 μM

Result	Reference
Higher doses suppressed T cell proliferation	Luo, 1992; Pross, 1992; ^b Klein, 1985; ^c Specter, 1990; ^d Lee, 1995; ^a Herring, 1998
Lower doses increased T cell proliferation <i>in vitro</i>	Luo, 1992; Lee, 1995; ^a Pross, 1992 ^b
Little or no effect on T cell proliferation	Lee, 1995; ^a Devane, 1992
Decreased B cell proliferation	Klein, 1985; ^c Lee, 1995 ^a
Increased B cell proliferation	Derocq, 1995
Antibody production suppressed	Baczynsky, 1983; Schatz, 1993
Antibody production suppressed	Titishov, 1989
Antibody production suppressed	Klein, 1990; Baczynsky, 1983; Kaminski, 1992, 1994; Herring, 1998
Repeated low doses or a high dose of THC suppressed the activity of natural killer cells	Patel, 1985; Klein, 1987
Doses of $\geq 10 \mu\text{M}$ suppressed natural killer cell cytolytic activity; doses $< 10 \mu\text{M}$ produced no effect	Klein, 1987; Luo, 1989
Variable doses of THC suppressed macrophage functions <i>in vitro</i>	Lopez-Cepero, 1986; Specter, 1991; Tang, 1992
THC suppressed normal immune response; interferons failed to increase when exposed to cytokine inducer; CBD had no suppressive effect	Cabral, 1986; Blanchard, 1986
Increased interferon production	Watzl, 1991
Decreased interferon production	
Both THC and CBD suppressed interleukin-2 secretion and number of interleukin-2 transcripts	Condie, 1996
Increased tumor necrosis factor production and interleukin-1 supernatant bioactivity	Shivers, 1994
Increased processing and release of interleukin-1 rather than cellular production of interleukin-1	Zhu, 1994
Increased interleukin-1 bioactivity	Klein, 1990

Continued

TABLE 2.7 *Continued*

Drug Tested	Cell Types Tested or Type of Animal Experiment	Drug Concentration*
THC	Drug and sublethal or lethal dose of <i>Legionella pneumophila</i> injected in mice	8 mg/kg before and after bacterial infection <5 mg/kg doses or one 8 mg/kg or 4 mg/kg dose before bacteria infection
THC	Drug and herpes simplex virus injected in immunodeficient mice	100 mg/kg before and after viral infection 100 mg/kg before viral infection

^aCell density dependent.

^bMitogen dependent.

^cDependent on serum concentration in cell culture medium.

^dDependent on timing of drug exposure relative to mitogen exposure.

*Drug concentrations are given in the standard format of molarity (M). A 1-M solution is the molecular weight of the compound (in grams) in 1 liter (L) of solution. The molecular

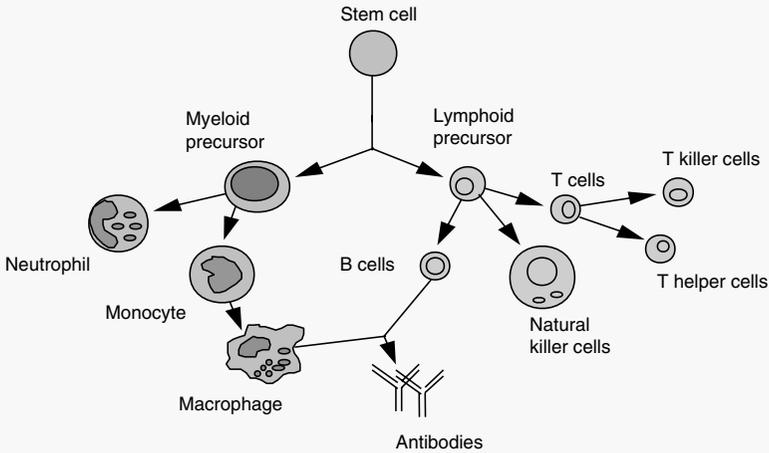
Box 2.1 Cells of the Immune System

The various organs of the immune system are positioned throughout the body and include bone marrow, thymus, lymph nodes, and spleen. The cells of the immune system consist of white blood cells, or leukocytes, which are formed in the bone marrow from stem cells—so-called because a great variety of cells descend from them (see below). There are two kinds of leukocytes: lymphocytes and phagocytes. *Lymphocytes* consist of B cells, T cells (B and T refer to where the cells mature, either in the bone marrow [B] or thymus [T]), and natural killer (NK) cells; the major phagocytes are monocytes, macrophages, and neutrophils. *Phagocytes* have many important roles in the immune response; most important is that they initiate the response by engulfing and digesting foreign substances, or antigens (such as bacteria, viruses, and foreign proteins), that enter the body. Once digested, the antigens are exposed to specialized lymphocytes, some of which produce antibodies and effector T cells, which help destroy any antigens remaining in the body. *Antibodies* are proteins produced by B cells that bind to antigens and promote antigen destruction. Effector T cells include killer T cells, which attack and kill antigen laden cells, and helper T cells, which secrete special proteins called cytokines that promote antigen elimination. NK cells are specialized lymphocytes that are also activated by antigen to either kill infected targets or secrete immunoregulatory cytokines.

Result	Reference
Cytokine-mediated septic shock and death occurred with exposure to sublethal dose of bacteria	Klein, 1993, 1994; Newton, 1994
Survival occurred, but with greater susceptibility to infection when challenged with bacteria and death when challenged with a lethal dose of bacteria	
Two high doses of THC potentiated the effects of herpes simplex and enhanced the progression of death	Specter, 1991
Single dose did not promote death	

weight of THC is 314, so a 1-M solution would be 314 g of THC in 1 L of solution, and a 10- μ M solution would be 3.14 mg THC/L.

A 1- to 10- μ M concentration will generally elicit a physiologically relevant response in immune cell cultures. Higher doses are often suspected of not being biologically meaningful because they are much larger than would ever be achieved in the body. The doses listed in this table are, for the most part, very high. See text for further discussion.



Cannabinoid Receptors and Intracellular Action in Immune Cells

CB₂ appears to be the predominant gene expressed in resting leukocytes.^{78,112} The level of CB₁ gene activity is normally low in resting cells but increases with cell activation.³² Thus the CB₁ receptor might be important only when immune responses are stimulated, but the physiological relevance of this observation remains to be determined. Some of the cannabinoid effects observed in immune systems, especially at high drug concentrations, are likely mediated through nonreceptor mechanisms, but these have not yet been identified.⁴

Ligand binding to either CB₁ or CB₂ inhibits adenylate cyclase, an enzyme that is responsible for cAMP production and is, thus, an integral aspect of intracellular signal transduction (see Figure 2.3).^{53,79,91,122,139,151,167} Increases in intracellular cAMP concentrations lead to immune enhancement, and decreases lead to an inhibition of the immune response.⁷⁷ Cannabinoids inhibit the rise in intracellular cAMP that normally results from leukocyte activation, and this might be the pathway through which cannabinoids suppress immune cell functions.^{28,74,167} In addition, cannabinoids activate other molecular pathways such as the nuclear factor-kB pathway, and therefore these signals might be modified in drug-treated immune cells.^{33,74}

T and B Cells

When stimulated by antigen, lymphocytes (see Box 2.1) first proliferate and then mature or differentiate to become potent effector cells, such as B cells that release antibodies or T cells that release cytokines. The normal T-cell proliferation that is seen when human lymphocytes and mouse splenocytes (spleen cells) are exposed to antigens and mitogens* can be inhibited by THC, 11-OH-THC, cannabinol, and 2-AG, as well as synthetic cannabinoid agonists such as CP 55,940; WIN 55,212-2; and HU-210.^{61,89,93,99,127,155} In contrast, one study testing anandamide revealed little or no effect on T cell proliferation.⁹³

However, these drug effects are variable and depend on experimental conditions, such as the experimental drug dose used, the mitogen used, the percentage of serum in the culture, and the timing of cannabinoid drug exposure. In general, lower doses of cannabinoids increase proliferation and higher doses suppress proliferation. Doses that are effective in suppressing immune function are typically greater than 10 μ M in cell culture studies and greater than 5 mg/kg in whole-animal studies.⁸⁵ By

*Mitogens are substances that stimulate cell division (mitosis) and cell transformation.

comparison, at 0.05 mg/kg, people will experience the full psychoactive effects of THC; however, because of their high metabolic rates, small rodents frequently require drug doses that are 100-fold higher than doses needed for humans to achieve comparable drug effects. Thus, the immune effects of doses of cannabinoids higher than those ever experienced by humans should be interpreted with caution.⁹³

As with T cells, B cell proliferation can be suppressed by various cannabinoids, such as THC, 11-OH-THC, and 2-AG, but B cell proliferation is more inhibited at lower drug concentrations than T cell proliferation.^{89,93} Conversely, low doses of THC, CP 55,940 and WIN 55,212-2 *increase* B cell proliferation in cultured human cells exposed to mitogen.³⁵ This effect possibly involves the CB₂ receptor, because the effect appears to be the same when the CB₁ receptor was blocked by the antagonist SR 141716A (which does not block the CB₂ receptor). The reason for the differences in B cell responsiveness to cannabinoids is probably due to differences in cell type and source; for example, B cells collected from mouse spleen might respond to cannabinoids somewhat differently than B cells from human tonsils.

Natural Killer Cells

Repeated injections of relatively low doses of THC (3 mg/kg/day^{121*}) or two injections of a high dose (40 mg/kg⁸⁶) suppress the ability of NK cells to destroy foreign cells in rats and mice. THC can also suppress cytolytic activity of the NK cells in cell cultures; 11-OH-THC is even more potent.⁸⁶ In contrast, THC concentrations below 10 μ M had no effect on NK cell activity in mouse cell cultures.⁹⁸

Macrophages

Macrophages perform various functions, including phagocytosis (ingestion and destruction of foreign substances), cytolysis, antigen presentation to lymphocytes, and production of active proteins involved in destroying microorganisms, tissue repair, and modulation of immune cells. Those functions can be suppressed by THC doses similar to those capable of modulating lymphocyte functions (see above).^{88,109}

*While 3 mg/kg would be a high dose for humans (see Table 3.1), in rodents, it is a low dose for immunological effects and a moderate dose for behavioral effects.

Cytokines

Cytokines are proteins produced by immune cells. When released from the producing cell, they can alter the function of other cells they come in contact with. In a sense they are like hormones. Thus, cannabinoids can either increase or decrease cytokine production depending upon experimental conditions.

Some cytokines, such as interferon- γ and interleukin-2 (IL-2), are produced by T helper-1 (Th1) cells. These cytokines help to activate cell-mediated immunity and the killer cells that eliminate microorganisms from the body (see Box 2.1). When injected into mice, THC suppresses the production of those cytokines that modulate the host response to infection (see below).¹¹⁵ Cannabinoids also modulate interferons induced by viral infection,²¹ as well as other interferon inducers.⁸⁵ Furthermore, in human cell cultures, interferon production can be increased by low concentrations but decreased by high concentrations of either THC or CBD.¹⁶⁸ In addition to Th1 cytokines, cannabinoids modulate the production of cytokines such as interleukin-1 (IL-1), tumor necrosis factor (TNF), and interleukin-6 (IL-6).^{145,176} At 8 mg/kg, THC can increase the *in vivo* mobilization of serum acute-phase cytokines, including IL-1, TNF, and IL-6.⁹⁰ Finally, although these studies suggest that cannabinoids can induce an increase in cytokines, other studies suggest that they can also suppress cytokine production.⁸⁵ The different results might be due to different cell culture conditions or because different cell lines were studied.

Antibody Production

Antibody production is an important measure of humoral immune function as contrasted with cellular (cell-mediated) immunity. Antibody production can be suppressed in mice injected with relatively low doses of THC (>5 mg/kg) or HU-210 (>0.05 mg/kg) and in mouse spleen cell cultures exposed to a variety of cannabinoids, including THC, 11-OH-THC, cannabinal, cannabidiol, CP 55,940, or HU-210.^{5,6,61,78,79,84,85,142,164} However, the inhibition of antibody response by cannabinoids was only observed when antibody-forming cells were exposed to T-cell-dependent antigens (the responses require functional T cells and macrophages as accessory cells). Conversely, antibody responses to several T-cell-independent antigens were not inhibited by THC; this suggests that B cells are relatively insensitive to inhibition by cannabinoids.¹⁴²

Resistance to Infection in Animals Exposed to Cannabinoids

Evaluation of bacterial infections in mice that received injections of

THC can suppress resistance to infection, although the effect depends on the dose and timing of drug administration. Mice pretreated with THC (8 mg/kg) one day before infection with a sublethal dose of the pneumonia-causing bacteria *Legionella pneumophila* and then treated again one day after the infection with THC developed symptoms of cytokine-mediated septic shock and died; control mice that were not pretreated with THC became immune to repeated infection and survived the bacterial challenge.⁹⁰ If only one injection of THC was given or doses less than 5 mg/kg were used, all the mice survived the initial infection but failed to survive later challenge with a lethal dose of the bacteria; hence, these mice failed to develop immune memory in response to the initial sublethal infection.⁸⁷ Note that these are very high doses and are considerably higher than doses experienced by marijuana users (see Figure 3.1).¹¹⁵ In rats, doses of 4.0 mg/kg THC are aversive.⁹⁵

Few studies have been done to evaluate the effect of THC on viral infections, and this subject needs further study.²⁰ Compared to healthy animals, THC might have greater immunosuppressive effects in animals whose immune systems are severely weakened. For example, a very high dose of THC (100 mg/kg) given two days before and after herpes simplex virus infection was shown to be a cofactor with the virus in advancing the progression to death in an immunodeficient mouse model infected with a leukemia virus.⁸⁵ However, THC given as a single dose (100 mg/kg) two days before herpes simplex virus infection did not promote the progression to death. Hence, whether THC is immunosuppressive probably depends on the timing of THC exposure relative to an infection.

Antiinflammatory Effects

As discussed above, cannabinoid drugs can modulate the production of cytokines, which are central to inflammatory processes in the body. In addition, several studies have shown directly that cannabinoids can be antiinflammatory. For example, in rats with autoimmune encephalomyelitis (an experimental model used to study multiple sclerosis), cannabinoids were shown to attenuate the signs and the symptoms of central nervous system damage.^{100,172} (Some believe that nerve damage associated with multiple sclerosis is caused by an inflammatory reaction.) Likewise, the cannabinoid, HU-211, was shown to suppress brain inflammation that resulted from closed-head injury¹⁴⁶ or infectious meningitis⁷ in studies on rats. HU-211 is a synthetic cannabinoid that does not bind to cannabinoid receptors and is not psychoactive;⁷ thus, without direct evidence, the effects of marijuana cannot be assumed to include those of HU-211. CT-3, another atypical cannabinoid, suppresses acute and chronic joint inflammation in animals.¹⁷⁸ It is a nonpsychoactive synthetic deriva-

tive of 11-THC-oic acid (a breakdown product of THC) and does not appear to bind to cannabinoid receptors.¹²⁹ Cannabichromene, a cannabinoid found in marijuana, has also been reported to have antiinflammatory properties.¹⁷³ No mechanism of action for possible antiinflammatory effects of cannabinoids has been identified, and the effects of these atypical cannabinoids and effects of marijuana are not yet established.

It is interesting to note that two reports of cannabinoid-induced analgesia are based on the ability of the endogenous cannabinoids, anandamide and PEA, to reduce pain associated with local inflammation that was experimentally induced by subcutaneous injections of dilute formalin.^{22,73} Both THC and anandamide can increase serum levels of ACTH and corticosterone in animals.¹⁶⁹ Those hormones are involved in regulating many responses in the body, including those to inflammation. The possible link between experimental cannabinoid-induced analgesia and reported antiinflammatory effects of cannabinoids is important for potential therapeutic uses of cannabinoid drugs but has not yet been established.

Conclusions Regarding Effects on the Immune System

Cell culture and animal studies have established cannabinoids as immunomodulators—that is, they increase some immune responses and decrease others. The variable responses depend on such experimental factors as drug dose, timing of delivery, and type of immune cell examined. Cannabinoids affect multiple cellular targets in the immune system and a variety of effector functions. Many of the effects noted above appear to occur at concentrations over 5 μM *in vitro* and over 5 $\mu\text{g}/\text{kg}$ *in vivo*.^{*} By comparison, a 5-mg injection of THC into a person (about 0.06 mg/kg) is enough to produce strong psychoactive effects. It should be emphasized, however, that little is known about the immune effects of chronic low-dose exposure to cannabinoids.

Another issue in need of further clarification involves the potential usefulness of cannabinoids as therapeutic agents in inflammatory diseases. Glucocorticoids have historically been used for these diseases, but nonpsychotropic cannabinoids potentially have fewer side effects and might thus offer an improvement over glucocorticoids in treating inflammatory diseases.

^{*}*In vitro* studies are those in which animal cells or tissue are removed and studied outside the animal; *in vivo* studies are those in which experiments are conducted in the whole animal.

TABLE 2.8 Historical Comparisons Between Cannabinoids and Opiates

Pharmacological Discoveries	Cannabinoids	Opiates
Discovery of receptor existence	1988 (Devane et al. and Dill and Howlett) ^{36,40}	1973 (Pert and Snyder, Simon, and Terenius) ^{123,149,162}
Identification of receptor antagonist	1994 SR 141716A (Rinaldi-Carmona et al.) ¹³²	Before 1973: naloxone
Discovery of first endogenous ligand	1992 anandamide (Devane et al.) ³⁷	1975 met- and leu-enkephalin (Hughes et al.) ⁷⁰
First receptor cloned	1990 (Matsuda et al.) ¹⁰⁷	1992 (Evans et al. and Kieffer et al.) ^{41,82}
Natural functions	Unknown	Pain, reproduction, mood, movement, and others

CONCLUSIONS AND RECOMMENDATIONS

Given the progress of the past 15 years in understanding the effects of cannabinoids, research in the next decade is likely to reveal even more. It is interesting to compare how little we know about cannabinoids with how much we know about opiates. Table 2.8 suggests good reason for optimism about the future of cannabinoid drug development. Now that many of the basic tools of cannabinoid pharmacology and biology have been developed, one can expect to see rapid advances that can begin to match what is known of opiate systems in the brain.

Despite the tremendous progress in understanding the pharmacology and neurobiology of brain cannabinoid systems, this field is still in its early developmental stages. A key focus for future study is the neurobiology of endogenous cannabinoids; establishing the precise brain localization (in which cells and where) of cannabinoids, cellular storage and release mechanisms, and uptake mechanisms will be crucial in determining the biological role of this system. Technology needed to establish the biological significance of these systems will be broad based and include such research tools as the transgenic or gene knockout mice, as has already been accomplished for various opioid-receptor types.²⁶ In 1997, both CB₁ and CB₂ knockout mice were generated by a team of scientists at the National Institutes of Health, and a group in France has developed another strain of CB₁ knockout mice.⁹²

Several research tools will greatly aid such investigations, in particular a greater selection of agonists and antagonists that permit discrimination in activation between CB₁ and CB₂ and hydrophilic agonists that can be delivered to animals or cells more effectively than hydrophobic compounds. In the area of drug development, future progress should continue to provide more specific agonists and antagonists for CB₁ and CB₂ receptors, with varying potential for therapeutic uses.

There are certain areas that will provide keys to a better understanding of the potential therapeutic value of cannabinoids. For example, basic biology indicates a role for cannabinoids in pain and control of movement, which is consistent with a possible therapeutic role in these areas. The evidence is relatively strong for the treatment of pain and, intriguing although less well established, for movement disorders. The neuroprotective properties of cannabinoids might prove therapeutically useful, although it should be noted that this is a new area and other, better studied, neuroprotective drugs have not yet been shown to be therapeutically useful. Cannabinoid research is clearly relevant not only to drug abuse but also to understanding basic human biology. Further, it offers the potential for the discovery and development of new therapeutically useful drugs.

CONCLUSION: At this point, our knowledge about the biology of marijuana and cannabinoids allows us to make some general conclusions:

- Cannabinoids likely have a natural role in pain modulation, control of movement, and memory.
- The natural role of cannabinoids in immune systems is likely multi-faceted and remains unclear.
- The brain develops tolerance to cannabinoids.
- Animal research has demonstrated the potential for dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine, or nicotine.
- Withdrawal symptoms can be observed in animals but appear mild compared with those of withdrawal from opiates or benzodiazepines, such as diazepam (Valium).

CONCLUSION: The different cannabinoid receptor types found in the body appear to play different roles in normal physiology. In addition, some effects of cannabinoids appear to be independent of those receptors. The variety of mechanisms through which cannabinoids can influence human physiology underlies the variety

of potential therapeutic uses for drugs that might act selectively on different cannabinoid systems.

RECOMMENDATION: Research should continue into the physiological effects of synthetic and plant-derived cannabinoids and the natural function of cannabinoids found in the body. Because different cannabinoids appear to have different effects, cannabinoid research should include, but not be restricted to, effects attributable to THC alone.

This chapter has summarized recent progress in understanding the basic biology of cannabinoids and provides a foundation for the next two chapters which review studies on the potential health risks (chapter 3) and benefits of marijuana use (chapter 4).

REFERENCES

1. Abood ME, Martin BR. 1996. Molecular neurobiology of the cannabinoid receptor. *International Review of Neurobiology* 39:197–221.
2. Abood ME, Sauss C, Fan F, Tilton CL, Martin BR. 1993. Development of behavioral tolerance to delta 9-THC without alteration of cannabinoid receptor binding or mRNA levels in whole brain. *Pharmacology, Biochemistry and Behavior* 46:575–579.
3. Aceto MD, Scates SM, Lowe JA, Martin BR. 1995. Cannabinoid precipitated withdrawal by the selective cannabinoid receptor antagonist, SR 141716A. *European Journal of Pharmacology* 282:R1–R2.
4. Adams IB, Martin BR. 1996. Cannabis: Pharmacology and toxicology in animals and humans. *Addiction* 91:1585–1614.
5. Baczynsky WO, Zimmerman AM. 1983a. Effects of delta-9-tetrahydrocannabinol, cannabiniol, and cannabidiol on the immune system in mice: I. In vivo investigation of the primary and secondary immune response. *Pharmacology* 26:1–11.
6. Baczynsky WO, Zimmerman AM. 1983b. Effects of delta 9-tetrahydrocannabinol, cannabiniol and cannabidiol on the immune system in mice. II. In vitro investigation using cultured mouse splenocytes. *Pharmacology* 26:12–19.
7. Bass R, Engelhard D, Trembovler V, Shohami E. 1996. A novel nonpsychotropic cannabinoid, HU-211, in the treatment of experimental pneumococcal meningitis. *Journal of Infectious Diseases* 173:735–738.
8. Beardsley PM, Balster RL, Harris LS. 1986. Dependence on tetrahydrocannabinol in rhesus monkeys. *Journal of Pharmacology and Experimental Therapeutics* 239:311–319.
9. Ben-Shabat S, Frider E, Sheskin T, Tamiri T, Rhee MH, Vogel Z, Bisogno T, De Petrocellis L, Di Marzo V, Mechoulam R. 1998. An entourage effect: Inactive endogenous fatty acid glycerol esters enhance 2-arachidonoyl-glycerol cannabinoid activity. *European Journal of Pharmacology* 353:23–31.
10. Bennett GJ. 1994. Neuropathic pain. In: Wall PD, Melzack R, Editors, *Textbook of Pain*. Edinburgh: Churchill Livingstone.
11. Bird KD, Boleyn T, Chesher GB, Jackson DM, Starmer GA, Teo RKC. 1980. Inter-cannabinoid and cannabinoid-ethanol interactions and their effects on human performance. *Psychopharmacology* 71:181–188.

12. Bloom AS, Dewey WL, Harris LS, Brosius KK. 1977. 9-nor-9b-hydroxyhexahydrocannabinol, a cannabinoid with potent antinociceptive activity: Comparisons with morphine. *Journal of Pharmacology and Experimental Therapeutics* 200:263–270.
13. Bornheim LM, Everhart ET, Li J, Correia MA. 1994. Induction and genetic regulation of mouse hepatic cytochrome P450 by cannabidiol. *Biochemical Pharmacology (England)* 48:161–171.
14. Bornheim LM, Kim KY, Chen B, Correia MA. 1993. The effect of cannabidiol on mouse hepatic microsomal cytochrome P450-dependent anandamide metabolism. *Biochemical and Biophysical Research Communications (United States)* 197:740–746.
15. Bornheim LM, Kim KY, Li J, Perotti BY, Benet LZ. 1995. Effect of cannabidiol pretreatment on the kinetics of tetrahydrocannabinol metabolites in mouse brain. *Drug Metabolism and Disposition (United States)* 23:825–831.
16. Breivogel CS, Sim LJ, Childers SR. 1997. Regional differences in cannabinoid receptor/G-protein coupling in rat brain. *Journal of Pharmacology and Experimental Therapeutics* 282:1632–1642.
17. British Medical Association. 1997. *Therapeutic Uses of Cannabis*. Amsterdam, The Netherlands: Harwood Academic Publishers.
18. Burkey TH, Quock RM, Consroe P, Roeske WR, Yamamura HI. 1997. Delta-9-tetrahydrocannabinol is a partial agonist of cannabinoid receptors in mouse brain. *European Journal of Pharmacology* 323:R3–R4.
19. Buxbaum DM. 1972. Analgesic activity of Δ^9 -tetrahydrocannabinol in the rat and mouse. *Psychopharmacology* 25:275–280.
20. Cabral GA, Dove Pettit DA. 1998. Drugs and immunity: Cannabinoids and their role in decreased resistance to infectious disease. *Journal of Neuroimmunology* 83:116–123.
21. Cabral GA, Lockmuller JC, Mishkin EM. 1986. Delta-9-tetrahydrocannabinol decreases alpha/beta interferon response to herpes simplex virus type 2 in the B6C3F1 mouse. *Proceedings of the Society for Experimental Biology and Medicine* 181:305–311.
22. Calignano A, La Rana G, Giuffrida A, Piomelli D. 1998. Control of pain initiation by endogenous cannabinoids. *Nature* 394:277–281.
23. Campbell KA, Foster TC, Hampson RE, Deadwyler SA. 1986a. Delta-9-tetrahydrocannabinol differentially affects sensory-evoked potentials in the rat dentate gyrus. *Journal of Pharmacology and Experimental Therapeutics* 239:936–940.
24. Campbell KA, Foster TC, Hampson RE, Deadwyler SA. 1986b. Effects of delta-9-tetrahydrocannabinol on sensory-evoked discharges of granule cells in the dentate gyrus of behaving rats. *Journal of Pharmacology and Experimental Therapeutics* 239:941–945.
25. Chen J, Marmur R, Pulles A, Paredes W, Gardner EL. 1993. Ventral tegmental microinjection of delta-9-tetrahydrocannabinol enhances ventral tegmental somatodendritic dopamine levels but not forebrain dopamine levels: Evidence for local neural action by marijuana's psychoactive ingredient. *Brain Research* 621:65–70.
26. Childers SR. 1997. Opioid receptors: Pinning down the opiate targets. *Current Biology* 7:R695–R697.
27. Childers SR, Breivogel CS. 1998. Cannabis and endogenous cannabinoid systems. *Drug and Alcohol Dependence* 51:173–187.
28. Coffey RG, Yamamoto Y, Shella E, Pross S. 1996. Tetrahydrocannabinol inhibition of macrophage nitric oxide production. *Biochemical Pharmacology* 52:743–751.
29. Collins DR, Pertwee RG, Davies SN. 1994. The action of synthetic cannabinoids on the induction of long-term potentiation in the rat hippocampal slice. *European Journal of Pharmacology* 259:R7–R8.

30. Collins DR, Pertwee RG, Davies SN. 1995. Prevention by the cannabinoid antagonist, SR141716A, of cannabinoid-mediated blockade of long-term potentiation in the rat hippocampal slice. *British Journal of Pharmacology* 115:869–870.
31. Costa B, Parolaro D, Colleoni M. 1996. Chronic cannabinoid, CP-55,940, administration alters biotransformation in the rat. *European Journal of Pharmacology* 313:17–24.
32. Daaka Y, Friedman H, Klein T. 1996. Cannabinoid receptor proteins are increased in Jurkat, human T-cell line after mitogen activation. *Journal of Pharmacology and Experimental Therapeutics* 276:776–783.
33. Daaka Y, Zhu W, Friedman H, Klein T. 1997. Induction of interleukin-2 receptor α gene by Δ^9 -tetrahydrocannabinol is mediated by nuclear factor κ B and CB₁ cannabinoid receptor. *DNA and Cell Biology* 16:301–309.
34. Deadwyler SA, Heyser CJ, Hampson RE. 1995. Complete adaptation to the memory disruptive effects of delta-9-THC following 35 days of exposure. *Neuroscience Research Communications* 17:9–18.
35. Derocq JM, Segui M, Marchand J, Le Fur G, Casellas P. 1995. Cannabinoids enhance human B-cell growth at low nanomolar concentrations. *FEBS Letters* 369:177–182.
36. Devane WA, Dysarc FA, Johnson MR, Melvin LS, Howlett AC. 1988. Determination and characterization of a cannabinoid receptor in rat brain. *Molecular Pharmacology* 34:605–613.
37. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffing F, Gibson D, Mandelbaum A, Etinger A, Mechoulam R. 1992. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 258:1946–1949.
38. Dewey WL. 1986. Cannabinoid pharmacology. *Pharmacology Review* 38:151–178.
39. Di Chiara G, Imperato A. 1988. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proceedings of the National Academy of Sciences, USA* 85:5274–5278.
40. Dill JA, Howlett AC. 1988. Regulation of adenylate cyclase by chronic exposure to cannabimimetic drugs. *Journal of Pharmacology and Experimental Therapeutics* 244:1157–1163.
41. Evans DJ, Keith DEJ, Morrison H, Magendzo K, Edwards RH. 1992. Cloning of a delta opioid receptor by functional expression. *Science* 258:1952–1955.
42. Fan F, Tao Q, Abood ME, Martin BR. 1996. Cannabinoid receptor down-regulation without alteration of the inhibitory effect of CP 55,940 on adenylyl cyclase in the cerebellum of CP 55,940-tolerant mice. *Brain Research* 706:13–20.
43. Felder CC, Glass M. 1998. Cannabinoid receptors and their endogenous agonists. *Annual Reviews of Pharmacology and Toxicology* 38:179–200.
44. Felder CC, Nielsen A, Briley EM, Palkovits M, Priller J, Axelrod J, Nguyen DN, Richardson JM, Riggan RM, Koppel GA, Paul SM, Becker GW. 1996. Isolation and measurement of the endogenous cannabinoid receptor agonist, anandamide, in brain and peripheral tissues of human and rat. *FEBS Letters* 393:231–235.
45. Fields HL. 1987. *Pain*. New York: McGraw-Hill.
46. Formukong EA, Evans AT, Evans FJ. 1988. Analgesic and antiinflammatory activity of constituents of *Cannabis sativa* L. *Inflammation* 12:361–371.
47. French ED. 1997. Delta-9-tetrahydrocannabinol excites rat VTA dopamine neurons through activation of cannabinoid CB₁ but not opioid receptors. *Neuroscience Letters* 226:159–162.
48. Galiege S, Mary S, Marchand J, Dussossoy D, Carriere D, Carayon P, Bouaboula M, Shire D, Le Fur G, Casellas P. 1995. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *European Journal of Biochemistry* 232:54–61.

49. Gessa GL, Mascia MS, Casu MA, Carta G. 1997. Inhibition of hippocampal acetylcholine release by cannabinoids: Reversal by SR 141716A. *European Journal of Pharmacology* 327:R1–R2.
50. Gifford AN, Ashby Jr CR. 1996. Electrically evoked acetylcholine release from hippocampal slices is inhibited by the cannabinoid receptor agonist, WIN 55212-2, and is potentiated by the cannabinoid antagonist, SR 141716A. *Journal of Pharmacology and Experimental Therapeutics* 277:1431–1436.
51. Gifford AN, Gardner EL, Ashby CRJ. 1997. The effect of intravenous administration of delta-9-tetrahydrocannabinol on the activity of A10 dopamine neurons recorded *in vivo* in anesthetized rats. *Neuropsychobiology* 36:96–99.
52. Glass M, Dragunow M, Faull RLM. 1997. Cannabinoid receptors in the human brain: A detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. *Neuroscience* 77:299–318.
53. Hadden JW, Hadden EM, Haddox MK, Goldberg ND. 1972. Guanosine 3':5'-cyclic monophosphates: A possible intracellular mediator of mitogenic influences in lymphocytes. *Proceedings of the National Academy of Sciences, USA* 69:3024–3027.
54. Hampson AJ, Grimaldi M, Axelrod J, Wink D. 1998. Cannabidiol and (-)delta-9-tetrahydrocannabinol are neuroprotective antioxidants. *Proceedings of the National Academy of Sciences, USA* 95:8268–8273.
55. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. 1999. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology* 141:385–394.
56. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. 1999. Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology* 141:395–404.
57. Herkenham M. 1995. Localization of cannabinoid receptors in brain and periphery. In: Pertwee RG, Editor, *Cannabinoid Receptors*. New York: Academic Press. Pp. 145–166.
58. Herkenham M, Lynn AB, de Costa BR, Richfield EK. 1991a. Neuronal localization of cannabinoid receptors in the basal ganglia of the rat. *Brain Research* 547:267–274.
59. Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa BR, Rice KC. 1991b. Characterization and localization of cannabinoid receptors in rat brain: A quantitative *in vitro* autoradiographic study. *Journal of Neuroscience* 11:563–583.
60. Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa BR, Rice KC. 1990. Cannabinoid receptor localization in the brain. *Proceedings of the National Academy of Sciences, USA* 87:1932–1936.
61. Herring AC, Koh WS, Kaminski NE. 1998. Inhibition of the cyclic AMP signaling cascade and nuclear factor binding to CRE and kappa B elements by cannabinol, a minimally CNS-active cannabinoid. *Biochemical Pharmacology* 55:1013–1023.
62. Herzberg U, Eliav E, Bennett GJ, Kopin IJ. 1997. The analgesic effects of R(+)-WIN 55,212-2 mesylate, a high affinity cannabinoid agonist, in a rat model of neuropathic pain. *Neuroscience Letters* 221:157–160.
63. Heyser CJ, Hampson RE, Deadwyler SA. 1993. Effects of delta-9-tetrahydrocannabinol on delayed match to sample performance in rats: Alterations in short-term memory associated with changes in task-specific firing of hippocampal cells. *Journal of Pharmacology and Experimental Therapeutics* 264:294–307.
64. Hohmann AG, Briley EM, Herkenham M. 1999. Pre- and postsynaptic distribution of cannabinoid and mu opioid receptors in rat spinal cord. *Brain Research* 822:17–25.
65. Hohmann AG, Herkenham M. 1998. Regulation of cannabinoid and mu opioid receptor binding sites following neonatal capsaicin treatment. *Neuroscience Letters* 252:13–16.

66. Hohmann AG, Herkenham M. 1999. Localization of central cannabinoid CB1 receptor mRNA in neuronal subpopulations of rat dorsal root ganglia: A double-label *in situ* hybridization study. *Neuroscience* 90:923–931.
67. Hohmann AG, Martin WJ, Tsou K, Walker JM. 1995. Inhibition of noxious stimulus-evoked activity of spinal cord dorsal horn neurons by the cannabinoid WIN 55,212-2. *Life Sciences* 56:2111–2119.
68. Hollister LE. 1986. Health aspects of cannabis. *Pharmacological Reviews* 38:1–20.
69. Hollister LE, Gillespie BA. 1975. Interactions in man of delta-9-THC. II. Cannabinol and cannabidiol. *Clinical Pharmacology and Therapeutics* 18:80–83.
70. Hughes J, Smith TW, Kosterlitz HW, Fothergill LA, Morgan BA, Morris HR. 1975. Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature* 258:577–580.
71. Jackson AL, Murphy LL. 1997. Role of the hypothalamic-pituitary-adrenal axis in the suppression of luteinizing hormone release by delta-9-tetrahydrocannabinol. *Neuroendocrinology* 65:446–452.
72. Jacob J, Ramabadran K, Campos-Medeiros M. 1981. A pharmacological analysis of levonantradol antinociception in mice. *Journal of Clinical Pharmacology* 21:327S–333S.
73. Jaggar SI, Hasnie FS, Sellaturay S, Rice AS. 1998. The anti-hyperalgesic actions of the cannabinoid anandamide and the putative CB₂ receptor agonist palmitoylethanolamide in visceral and somatic inflammatory pain. *Pain* 76:189–199.
74. Jeon YJ, Yang K-H, Pulaski JT, Kaminski NE. 1996. Attenuation of inducible nitric oxide synthase gene expression by delta-9-tetrahydrocannabinol is mediated through the inhibition of nuclear factor- κ B/Rel activation. *Molecular Pharmacology* 50:334–341.
75. Johnson MR, Melvin LS. 1986. The discovery of non-classical cannabinoid analgesics. In: Mechoulam R, Editor, *Cannabinoids as Therapeutic Agents*. Boca Raton, FL: CRC Press, Inc. Pp. 121–145.
76. Jones RT, Benowitz NL, Herning RI. 1981. Clinical relevance of cannabis tolerance and dependence. *Journal of Clinical Pharmacology* 21:143S–152S.
77. Kaminski NE. 1996. Immune regulation by cannabinoid compounds through the inhibition of the cyclic AMP signaling cascade and altered gene expression. *Biochemical Pharmacology* 52:1133–1140.
78. Kaminski NE, Abood ME, Kessler FK, Martin BR, Schatz AR. 1992. Identification of a functionally relevant cannabinoid receptor on mouse spleen cells that is involved in cannabinoid-mediated immune modulation. *Molecular Pharmacology* 42:736–742.
79. Kaminski NE, Koh WS, Yang KH, Lee M, Kessler FK. 1994. Suppression of the humoral immune response by cannabinoids is partially mediated through inhibition of adenylate cyclase by a pertussis toxin-sensitive G-protein coupled mechanism. *Biochemical Pharmacology* 48:1899–1908.
80. Kaminski NE. 1998. Regulation of cAMP cascade, gene expression and immune function by cannabinoid receptors. *Journal of Neuroimmunology* 83:124–132.
81. Karniol IG, Shirakawa I, Kasinski N, Pfeferman A, Carlini EA. 1975. Cannabidiol interferes with the effects of delta-9-tetrahydrocannabinol in man. *European Journal of Pharmacology* 28:172–177.
82. Kieffer BL, Befort K, Gaveriaux-Ruff C, Hirth CG. 1992. The delta-opioid receptor: Isolation of a cDNA by expression cloning and pharmacological characterization. *Proceedings of the National Academy of Sciences, USA* 89:12048–12052.
83. Kirby MT, Hampson RE, Deadwyler SA. 1995. Cannabinoids selectively decrease paired-pulse perforant path synaptic potentials in the dentate gyrus *in vitro*. *Brain Research* 688:114–120.

84. Klein TW, Friedman H. 1990. Modulation of murine immune cell function by marijuana components. In: Watson R, Editor, *Drugs of Abuse and Immune Function*. Boca Raton, FL: CRC Press.
85. Klein TW, Friedman H, Specter SC. 1998. Marijuana, immunity and infection. *Journal of Neuroimmunology* 83:102–115.
86. Klein TW, Newton C, Friedman H. 1987. Inhibition of natural killer cell function by marijuana components. *Journal of Toxicology and Environmental Health* 20:321–332.
87. Klein TW, Newton C, Friedman H. 1994. Resistance to *Legionella pneumophila* suppressed by the marijuana component, tetrahydrocannabinol. *Journal of Infectious Diseases* 169:1177–1179.
88. Klein TW, Newton C, Friedman H. 1998. Cannabinoid receptors and immunity. *Immunology Today* 19:373–381.
89. Klein TW, Newton C, Widen R, Friedman H. 1985. The effect of delta-9-tetrahydrocannabinol and 11-hydroxy-delta-9-tetrahydrocannabinol on T-lymphocyte and B-lymphocyte mitogen responses. *Journal of Immunopharmacology* 7:451–466.
90. Klein TW, Newton C, Widen R, Friedman H. 1993. Delta-9-tetrahydrocannabinol injection induces cytokine-mediated mortality of mice infected with *Legionella pneumophila*. *Journal of Pharmacology and Experimental Therapeutics* 267:635–640.
91. Koh WS, Yang KH, Kaminski NE. 1995. Cyclic AMP is an essential factor in immune responses. *Biochemical and Biophysical Research Communications* 206:703–709.
92. Ledent C, Valverde O, Cossu G, Petitot F, Aubert JF, Beslot F, Bohme GA, Imperato A, Pedrazzini T, Roques BP, Vassart G, Fratta W, Parmentier M. 1999. Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. *Science* 283:401–404.
93. Lee M, Yang KH, Kaminski NE. 1995. Effects of putative cannabinoid receptor ligands, anandamide and 2-arachidonyl-glycerol, on immune function in B6C3F1 mouse splenocytes. *Journal of Pharmacology and Experimental Therapeutics* 275:529–536.
94. Lepore M, Liu X, Savage V, Matalon D, Gardner EL. 1996. Genetic differences in delta 9-tetrahydrocannabinol-induced facilitation of brain stimulation reward as measured by a rate-frequency curve-shift electrical brain stimulation paradigm in three different rat strains. *Life Sciences* 58:365–372.
95. Lepore M, Vorel SR, Lowinson J, Gardner EL. 1995. Conditioned place preference induced by delta 9-tetrahydrocannabinol: Comparison with cocaine, morphine, and food reward. *Life Sciences* 56:2073–2080.
96. Lichtman AH, Martin BR. 1991a. Spinal and supraspinal components of cannabinoid-induced antinociception. *Journal of Pharmacology and Experimental Therapeutics* 258:517–523.
97. Little PJ, Compton DR, Mechoulam R, Martin BR. 1989. Stereochemical effects of 11-OH-delta-8-THC-dimethylheptyl in mice and dogs. *Pharmacology, Biochemistry Behavior* 32:661–666.
98. Lu F, Ou DW. 1989. Cocaine or delta-9-tetrahydrocannabinol does not affect cellular cytotoxicity *in vitro*. *International Journal of Pharmacology* 11:849–852.
99. Luo YD, Patel MK, Wiederhold MD, Ou DW. 1992. Effects of cannabinoids and cocaine on the mitogen-induced transformations of lymphocytes of human and mouse origins. *International Journal of Immunopharmacology* 14:49–56.
100. Lyman WD, Sonett JR, Brosnan CFER, Bornstein MB. 1989. Delta 9-tetrahydrocannabinol: A novel treatment for experimental autoimmune encephalomyelitis. *Journal of Neuroimmunology* 23:73–81.
101. Mailleux P, Vanderhaeghen JJ. 1992. Distribution of neuronal cannabinoid receptor in the adult rat brain: A comparative receptor binding radioautography and *in situ* hybridization histochemistry. *Neuroscience* 48:655–668.

102. Martin WJ, Hohmann AG, Walker JM. 1996. Suppression of noxious stimulus-evoked activity in the ventral posterolateral nucleus of the thalamus by a cannabinoid agonist: Correlation between electrophysiological and antinociceptive effects. *The Journal of Neuroscience* 16:6601–6611.
103. Martin WJ, Patrick SL, Coffin PO, Tsou K, Walker JM. 1995. An examination of the central sites of action of cannabinoid-induced antinociception in the rat. *Life Sciences* 56:2103–2109.
104. Martin WJ, Patrick SL, Coffin PO, Tsou K, Walker JM. 1995. An examination of the central sites of action of cannabinoid-induced antinociception in the rat. *Life Sciences* 56:2103–2109.
105. Martin WJ, Tsou K, Walker JM. 1998. Cannabinoid receptor-mediated inhibition of the rat tail-flick reflex after microinjections into the rostral ventromedial medulla. *Neuroscience Letters* 242:33–36.
106. Martoletta MC, Cossu G, Fattore L, Gessa GL, Fratta W. 1998. Self-administration of the cannabinoid receptor agonist WIN 55,212-2 in drug-naive mice. *Neuroscience* 85:327–330.
107. Matsuda L, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. 1990. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* 346:561–564.
108. Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NSA, Gopher A, Almog S, Martin BR, Compton D, Pertwee RG, Griffin G, Bayewitch M, Barg J, Vogel Z. 1995. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochemical Pharmacology* 50:83–90.
109. Mechoulam R, Hanus L, Fride E. 1998. Towards cannabinoid drugs—revisited. In: Ellis GP, Luscombe DK, Oxford AW, Editors, *Progress in Medicinal Chemistry*. v. 35. Amsterdam: Elsevier Science. Pp. 199–243.
110. Meng ID, Manning BH, Martin WJ, Fields HL. 1998. An analgesia circuit activated by cannabinoids. *Nature* 395:381–383.
111. Miller AS, Walker JM. 1996. Electrophysiological effects of a cannabinoid on neural activity in the globus pallidus. *European Journal of Pharmacology* 304:29–35.
112. Munro S, Thomas KL, Abu-Shaar M. 1993. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 365:61–65.
113. Murphy LL, Steger RW, Smith MS, Bartke A. 1990. Effects of delta-9-tetrahydrocannabinol, cannabidiol and cannabidiol, alone and in combinations, on luteinizing hormone and prolactin release and on hypothalamic neurotransmitters in the male rat. *Neuroendocrinology* 52:316–321.
114. Narimatsu S, Watanabe K, Matsunaga T, Yamamoto I, Imaoka S, Funae Y, Yoshimura H. 1993. Suppression of liver microsomal drug-metabolizing enzyme activities in adult female rats pretreated with cannabidiol. *Biological and Pharmaceutical Bulletin (Japan)* 16:428–430.
115. Newton CA, Klein T, Friedman H. 1994. Secondary immunity to *Legionella pneumophila* and Th1 activity are suppressed by delta-9-tetrahydrocannabinol injection. *Infection and Immunity* 62:4015–4020.
116. Norwicky AV, Teyler TJ, Vardaris RM. 1987. The modulation of long-term potentiation by delta-9-tetrahydrocannabinol in the rat hippocampus, in vitro. *Brain Research Bulletin* 19:663.
117. O'Leary D, Block RI, Flaum M, Boles Ponto LL, Watkins GL, Hichwa RD. 1998. Acute marijuana effects on rCBF and cognition: A PET study. *Abstracts—Society for Neuroscience: 28th Annual Meeting*. Los Angeles, November 7–12, 1998. Washington, DC: Society for Neuroscience.

118. Ohlsson A, Lindgren J-E, Wahlen A, Agurell S, Hollister LE, Gillespie HK. 1980. Plasma delta-9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clinical Pharmacology and Therapeutics* 28:409–416.
119. Oviedo A, Glowa J, Herkenham M. 1993. Chronic cannabinoid administration alters cannabinoid receptor binding in rat brain: A quantitative autoradiographic study. *Brain Research* 616:293–302.
120. Pacheco MA, Ward SJ, Childers SR. 1993. Identification of cannabinoid receptors in cultures of rat cerebellar granule cells. *Brain Research* 603:102–110.
121. Patel V, Borysenko M, Kumar MSA, Millard WJ. 1985. Effects of acute and subchronic delta-9-tetrahydrocannabinol administration on the plasma catecholamine, beta-endorphin, and corticosterone levels and splenic natural killer cell activity in rats. *Proceedings of the Society for Experimental Biology and Medicine* 180:400–404.
122. Pepe S, Ruggiero A, Tortora G, Ciaardiello F, Garbi C, Yokozaki H, Cho-Chung YS, Clair T, Skalhogg BS, Bianco AR. 1994. Flow cytometric detection of the RI alpha subunit of type-I cAMP-dependent protein kinase in human cells. *Cytometry* 15:73–79.
123. Pert CB, Snyder SH. 1973. Opiate receptor: Demonstration in nervous tissue. *Science* 179:1011–1014.
124. Pertwee RG. 1997b. Pharmacology of cannabinoid CB₁ and CB₂ receptors. *Pharmacology and Therapeutics* 74:129–180.
125. Pertwee RG, Stevenson LA, Griffin G. 1993. Cross-tolerance between delta-9-tetrahydrocannabinol and the cannabimimetic agents, CP 55,940, WIN 55,212-2 and anandamide [published erratum appears in *British Journal of Pharmacology*, 1994, 111(3):968]. *British Journal of Pharmacology* 110:1483–1490.
126. Pertwee RG, Wickens AP. 1991. Enhancement by chlordiazepoxide of catalepsy induced in rats by intravenous or intrapallidal injections of enantiomeric cannabinoids. *Neuropharmacology* 30:237–244.
127. Pross SH, Nakano Y, Widen R, McHugh S, Newton C, Klein TW, Friedman H. 1992. Differing effects of delta-9-tetrahydrocannabinol (THC) on murine spleen cell populations dependent upon stimulators. *International Journal of Immunopharmacology* 14:1019–1027.
128. Razdan RK. 1986. Structure-activity relationships in cannabinoids. *Pharmacology Review* 38:75–149.
129. Rhee MH, Vogel Z, Barg J, Bayewitch M, Levy R, Hanus L, Breuer A, Mechoulam R. 1997. Cannabinol derivatives: Binding to cannabinoid receptors and inhibition of adenylyl-cyclase. *Journal of Medicinal Chemistry* 40:3228–3233.
130. Richardson JD, Aanonsen L, Hargreaves KM. 1998. Hypoactivity of the spinal cannabinoid system results in NMDA-dependent hyperalgesia. *Journal of Neuroscience* 18:451–457.
131. Richardson JD, Kilo S, Hargreaves KM. 1998. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB₁ receptors. *Pain* 75:111–119.
132. Rinaldi-Carmona M, Barth F, Heaulme M, Shire D, Calandra B, Congy C, Martinez S, Maruani J, Neliat G, Caput D, Ferrara P, Soubrie P, Breliere JC, Le Fur G. 1994. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. *FEBS Letters* 350:240–244.
133. Rinaldi-Carmona M, Barth F, Millan J, Defrocq J, Casellas P, Congy C, Oustric D, Sarran M, Bouaboula M, Calandra B, Portier M, Shire D, Breliere J, Le Fur G. 1998. SR144528, the first potent and selective antagonist of the CB₂ cannabinoid receptor. *Journal of Pharmacology and Experimental Therapeutics* 284:644–650.

134. Rodríguez de Fonseca F, Fernández-Ruiz JJ, Murphy LL, Eldridge JC, Steger RW, Bartke A. 1991. Effects of delta-9-tetrahydrocannabinol exposure on adrenal medullary function: Evidence of an acute effect and development of tolerance in chronic treatments. *Pharmacology, Biochemistry and Behavior* 40:593–598.
135. Rodriguez de Fonseca F, Carrera MRA, Navarro M, Koob G, Weiss F. 1997. Activation of corticotropin-releasing factor in the limbic system during cannabinoid withdrawal [see comments *Science* 1997, 276:1967–1968]. *Science* 276:2050–2054.
136. Rodriguez de Fonseca F, Gorriti MA, Fernandez-Ruiz JJ, Palomo T, Ramos JA. 1994. Down-regulation of rat brain cannabinoid binding sites after chronic delta-9-tetrahydrocannabinol treatment. *Pharmacology, Biochemistry and Behavior* 47:33–40.
137. Romero J, García L, Fernández-Ruiz JJ, Cebeira M, Ramos JA. 1995. Changes in rat brain cannabinoid binding sites after acute or chronic exposure to their endogenous agonist, anandamide, or to delta-9-tetrahydrocannabinol. *Pharmacology, Biochemistry and Behavior* 51:731–737.
138. Romero J, Garcia-Palomero E, Castro JG, Garcia-Gil L, Ramos JA, Fernandez-Ruiz JJ. 1997. Effects of chronic exposure to delta-9-tetrahydrocannabinol on cannabinoid receptor binding and mRNA levels in several rat brain regions. *Molecular Brain Research* 46:100–108.
139. Russell DH. 1978. Type I cyclic AMP-dependent protein kinase as a positive effector of growth. *Advances in Cyclic Nucleotide Research* 9:493–506.
140. Sanudo-Pena MC, Tsou K, Delay ER, Hohmann AG, Force M, Walker JM. 1997. Endogenous cannabinoids as an aversive or counter-rewarding system in the rat. *Neuroscience Letters* 223:125–128.
141. Sanudo-Pena MC, Walker JM. 1997. Role of the subthalamic nucleus in cannabinoid actions in the substantia nigra of the rat. *Journal of Neurophysiology* 77:1635–1638.
142. Schatz AR, Koh WS, Kaminski NE. 1993. Delta-9-tetrahydrocannabinol selectively inhibits T-cell dependent humoral immune responses through direct inhibition of accessory T-cell function. *Immunopharmacology* 26:129–137.
143. Schlicker E, Timm J, Zenter J, Goethert M. 1997. Cannabinoid CB₁ receptor-mediated inhibition of noradrenaline release in the human and guinea-pig hippocampus. *Naunyn-Schmiedeberg's Archives of Pharmacology* 356:583–589.
144. Shen M, Piser TM, Seybold VS, Thayer SA. 1996. Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. *Journal of Neuroscience* 16:4322–4334.
145. Shivers SC, Newton C, Friedman H, Klein TW. 1994. Delta 9-tetrahydrocannabinol (THC) modulates IL-1 bioactivity in human monocyte/macrophage cell lines. *Life Sciences* 54:1281–1289.
146. Shohami E, Gallily R, Mechoulam R, Bass R, Ben-Hur T. 1997. Cytokine production in the brain following closed head injury: Dexanabinol (HU-211) is a novel TNF-alpha inhibitor and an effective neuroprotectant. *Journal of Neuroimmunology* 72:169–177.
147. Sim LJ, Hampson RE, Deadwyler SA, Childers SR. 1996. Effects of chronic treatment with delta-9-tetrahydrocannabinol on cannabinoid-stimulated [³⁵S]GTPyS autoradiography in rat brain. *Journal of Neuroscience* 16:8057–8066.
148. Sim LJ, Xiao R, Selley DE, Childers SR. 1996. Differences in G-protein activation by mu- and delta-opioid, and cannabinoid, receptors in rat striatum. *European Journal of Pharmacology* 307:97–105.
149. Simon EJ. 1973. In search of the opiate receptor. *American Journal of Medical Sciences* 266:160–168.

150. Skaper SD, Buriani A, Dal Toso R, Petrelli L, Romanello S, Facci L, Leon A. 1996. The ALIAmide palmitoylethanolamide and cannabinoids, but not anandamide, are protective in a delayed postglutamate paradigm of excitotoxic death in cerebellar granule neurons. *Proceedings of the National Academy of Sciences, USA* 93:3984–3989.
151. Smith JW, Steiner AL, Newberry WM, Parker CW. 1971. Cyclic adenosine 3',5'-monophosphate in human lymphocytes: Alteration after phytohemagglutinin. *Journal of Clinical Investigation* 50:432–441.
152. Smith PB, Compton DR, Welch SP, Razdan RK, Mechoulam R, Martin BR. 1994. The pharmacological activity of anandamide, a putative endogenous cannabinoid, in mice. *Journal of Pharmacology and Experimental Therapeutics* 270:219–227.
153. Smith PB, Welch SP, Martin BR. 1994. Interactions between delta 9-tetrahydrocannabinol and kappa opioids in mice. *Journal of Pharmacology and Experimental Therapeutics* 268: 1381–1387.
154. Sofia RD, Nalepa SD, Harakal JJ, Vassar HB. 1973. Anti-edema and analgesic properties of delta-9-tetrahydrocannabinol (THC). *Journal of Pharmacology and Experimental Therapeutics* 186:646–655.
155. Specter S, Lancz G, Hazelden J. 1990. Marijuana and immunity: Tetrahydrocannabinol mediated inhibition of lymphocyte blastogenesis. *International Journal of Immunopharmacology* 12:261–267.
156. Stefano G, Salzet B, Salzet M. 1997. Identification and characterization of the leech CNS cannabinoid receptor: Coupling to nitric oxide release. *Brain Research* 753:219–224.
157. Stella N, Schweitzer P, Piomelli D. 1997. A second endogenous cannabinoid that modulates long term potentiation. *Nature* 388:773–778.
158. Strangman NM, Patrick SL, Hohmann AG, Tsou K, Walker JM. 1998. Evidence for a role of endogenous cannabinoids in the modulation of acute and tonic pain sensitivity. *Brain Research* 813:323–328.
159. Sulcova E, Mechoulam R, Fride E. 1998. Biphasic effects of anandamide. *Pharmacology, Biochemistry and Behavior* 59:347–352.
160. Szabo B, Dorner L, Pfreundtner C, Norenberg W, Starke K. 1998. Inhibition of GABAergic inhibitory postsynaptic currents by cannabinoids in rat corpus striatum. *Neuroscience* 85:395–403.
161. Tanda G, Pontieri FE, Di Chiara G. 1997. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common $\mu 1$ opioid receptor mechanism. *Science* 276:2048–2049.
162. Terenius L. 1973. Characteristics of the "receptor" for narcotic analgesics in synaptic plasma membrane fraction from rat brain. *Acta Pharmacologica Et Toxicologica* 33:377–384.
163. Terranova JP, Michaud JC, Le Fur G, Soubrié P. 1995. Inhibition of long-term potentiation in rat hippocampal slice by anandamide and WIN55212-2: Reversal by SR141716 A, a selective antagonist of CB₁ cannabinoid receptors. *Naunyn-Schmiedeberg's Archives of Pharmacology* 352:576–579.
164. Titishov N, Mechoulam R, Zimmerman AM. 1989. Stereospecific effects of (-) and (+)-7-hydroxy-delta-6-tetrahydrocannabinol-dimethylheptyl on the immune system of mice. *Pharmacology* 39:337–349.
165. Tsou K, Brown S, Sanudo-Pena MC, Mackie K, Walker JM. 1998. Immunohistochemical distribution of cannabinoid CB₁ receptors in the rat central nervous system. *Neuroscience* 83:393–411.
166. Tsou K, Patrick SL, Walker JM. 1995. Physical withdrawal in rats tolerant to delta-9-tetrahydrocannabinol precipitated by a cannabinoid receptor antagonist. *European Journal of Pharmacology* 280:R13–R15.

167. Watson PF, Krupinski J, Kempinski A, Frankenfield C. 1994. Molecular cloning and characterization of the type VII isoform of mammalian adenylyl cyclase expressed widely in mouse tissues and in S49 mouse lymphoma cells. *Journal of Biological Chemistry* 269:28893–28898.
168. Watzl B, Scuder P, Watson RR. 1991. Marijuana components stimulate human peripheral blood mononuclear cell secretion of interferon-gamma and suppress interleukin-1 alpha in vitro. *International Journal of Immunopharmacology* 13:1091–1097.
169. Weidenfeld J, Feldman S, Mechoulam R. 1994. Effect of the brain constituent anandamide, a cannabinoid receptor agonist, on the hypothalamo-pituitary-adrenal axis in the rat. *Neuroendocrinology* 59:110–112.
170. Welch SP. 1993. Blockade of cannabinoid-induced antinociception by norbinaltorphimine, but not N,N-diallyl-tyrosine-Aib-phenylalanine-leucine, ICI 174,864 or naloxone in mice. *Journal of Pharmacology and Experimental Therapeutics* 265:633–640.
171. Welch SP, Thomas C, Patrick GS. 1995. Modulation of cannabinoid-induced antinociception after intracerebroventricular versus intrathecal administration to mice: Possible mechanisms for interaction with morphine. *Journal of Clinical and Experimental Therapeutics* 272:310–321.
172. Wirguin I, Mechoulam R, Breuer A, Schezen E, Weidenfeld J, Brenner T. 1994. Suppression of experimental autoimmune encephalomyelitis by cannabinoids. *Immunopharmacology* 28:209–214.
173. Wirth PW, Watson ES, ElSohly M, Turner CE, Murphy JC. 1980. Anti-inflammatory properties of cannabichromene. *Life Sciences* 26:1991–1995.
174. Yaksh TL. 1981. The antinociceptive effects of intrathecally administered levonantradol and desacetyl-levonantradol in the rat. *Journal of Clinical Pharmacology* 21:334S–340S.
175. Yoshida H, Usami N, Ohishi Y, Watanabe K, Yamamoto I, Yoshimura H. 1995. Synthesis and pharmacological effects in mice of halogenated cannabinol derivatives. *Chemical and Pharmaceutical Bulletin* 42:335–337.
176. Zhu W, Newton C, Daaka Y, Friedman H, Klein TW. 1994. Delta 9-tetrahydrocannabinol enhances the secretion of interleukin 1 from endotoxin-stimulated macrophages. *Journal of Pharmacology and Experimental Therapeutics* 270:1334–1339.
177. Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. 1982. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology (Berl)* 76:245–250.
178. Zurier RB, Rossetti RG, Lane JH, Goldberg JM, Hunter SA, Burstein SH. 1998. Dimethylheptyl-THC-11 oic acid: A non-psychoactive antiinflammatory agent with a cannabinoid template structure. *Arthritis and Rheumatism* 41:163–170.

3

First, Do No Harm: Consequences of Marijuana Use and Abuse



Primum non nocere. This is the physician's first rule: whatever treatment a physician prescribes to a patient—first, that treatment must not harm the patient.

The most contentious aspect of the medical marijuana debate is not whether marijuana can alleviate particular symptoms but rather the degree of harm associated with its use. This chapter explores the negative health consequences of marijuana use, first with respect to drug abuse, then from a psychological perspective, and finally from a physiological perspective.

THE MARIJUANA "HIGH"

The most commonly reported effects of smoked marijuana are a sense of well-being or euphoria and increased talkativeness and laughter alternating with periods of introspective dreaminess followed by lethargy and sleepiness (see reviews by Adams and Martin, 1996,¹ Hall and Solowij,⁵⁹ and Hall et al.⁶⁰). A characteristic feature of a marijuana "high" is a distortion in the sense of time associated with deficits in short-term memory and learning. A marijuana smoker typically has a sense of enhanced physical and emotional sensitivity, including a feeling of greater interpersonal closeness. The most obvious behavioral abnormality displayed by someone under the influence of marijuana is difficulty in carrying on an intelli-

gible conversation, perhaps because of an inability to remember what was just said even a few words earlier.

The high associated with marijuana is not generally claimed to be integral to its therapeutic value. But mood enhancement, anxiety reduction, and mild sedation can be desirable qualities in medications—particularly for patients suffering pain and anxiety. Thus, although the psychological effects of marijuana are merely side effects in the treatment of some symptoms, they might contribute directly to relief of other symptoms. They also must be monitored in controlled clinical trials to discern which effect of cannabinoids is beneficial. These possibilities are discussed later under the discussions of specific symptoms in chapter 4.

The effects of various doses and routes of delivery of THC are shown in Table 3.1.

Adverse Mood Reactions

Although euphoria is the more common reaction to smoking marijuana, adverse mood reactions can occur. Such reactions occur most frequently in inexperienced users after large doses of smoked or oral marijuana. They usually disappear within hours and respond well to reassurance and a supportive environment. Anxiety and paranoia are the most common acute adverse reactions;⁵⁹ others include panic, depression, dysphoria, depersonalization, delusions, illusions, and hallucinations.^{1,40,66,69} Of regular marijuana smokers, 17% report that they have experienced at least one of the symptoms, usually early in their use of marijuana.¹⁴⁵ Those observations are particularly relevant for the use of medical marijuana in people who have not previously used marijuana.

DRUG DYNAMICS

There are many misunderstandings about drug abuse and dependence (see reviews by O'Brien¹¹⁴ and Goldstein⁵⁴). The terms and concepts used in this report are as defined in the most recent *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*,³ the most influential system in the United States for diagnoses of mental disorders, including substance abuse (see Box 3.1). Tolerance, dependence, and withdrawal are often presumed to imply abuse or addiction, but this is not the case. Tolerance and dependence are *normal* physiological adaptations to repeated use of any drug. The correct use of prescribed medications for pain, anxiety, and even hypertension commonly produces tolerance and some measure of physiological dependence.

Even a patient who takes a medicine for appropriate medical indications and at the correct dosage can develop tolerance, physical depen-

TABLE 3.1 Psychoactive Doses of THC in Humans

Investigators	THC Delivery System	THC Dose Administered	Resulting Plasma Concentrations of THC	Subjects' Reactions
Heishman and co-workers (1990) ^{62a}	One 2.75% THC cigarette smoked	0.32 mg/kg ^a	50–100 ng/ml	At higher level, subjects felt 100% "high" and psychomotor performance was decreased; at 50 ng/ml, subjects felt about 50% "high"
Kelly and co-workers (1993) ⁸⁵	1-g marijuana cigarette smoked (2% or 3.5% THC)	0.25–0.50 mg/kg ^a	Not measured	Enough to feel psychological effects of THC
Ohlsson and co-workers (1980) ¹¹⁸	19-mg THC cigarette smoked (about 1.9% THC)	About 0.22 mg/kg ^b	100 ng/ml	Subjects felt "high"
	5 mg of THC injected intravenously	About 0.06 mg/kg ^b	100 ng/ml	Subjects felt "high"
	Chocolate chip cookie containing 20 mg of THC	About 0.24 mg/kg	8 ng/ml	Subjects rated "high" as only about 40%
Lindgren and co-workers (1981) ⁹⁵	19-mg THC cigarette smoked to "desired high"	12 mg smoked (7 mg remained in cigarette butt)	85 ng/ml after 3 min., 35 ng/ml after 15 min.	Subjects felt "high" after 3 min., and maximally high after 10–20 min. (average self-ratings of 5.5 on 10-point scale)
	5 mg of THC injected intravenously	0.06 mg/kg ^c	300 ng/ml after 3 min., 65 ng/ml after 15 min.	Subjects felt maximally "high" after 10 min. (average self ratings of 7.5 on a 10-point scale)

^aSubjects' weights and cigarette weights were not given. Calculation based on 85-kg body weight and 1-g cigarette weight. Note that some THC would have remained in the cigarette butt and some would have been lost in sidestream smoke, so these represent maximal possible doses. Actual doses would have been slightly less.

^bBased on estimated average 85-kg weight of 11 men 18–35 years old.

^cBased on approximate 80-kg weight of subjects (including men and women).

Box 3.1 Definitions

Addiction. Substance dependence.

Craving refers to the intense desire for a drug and is the most difficult aspect of addiction to overcome.

Physiological dependence is diagnosed when there is evidence of either tolerance or withdrawal; it is sometimes, but not always, manifested in substance dependence.

Reinforcement. A drug—or any other stimulus—is referred to as a reinforcer if exposure to it is followed by an increase in frequency of drug-seeking behavior. The taste of chocolate is a reinforcer for biting into a chocolate bar. Likewise, for many people the sensation experienced after drinking alcohol or smoking marijuana is a reinforcer.

Substance dependence is a cluster of cognitive, behavioral, and physiological symptoms indicating that a person continues use of the substance despite significant substance-related problems.

Tolerance is the most common response to repetitive use of a drug and can be defined as the reduction in responses to the drug after repeated administrations.

Withdrawal. The collective symptoms that occur when a drug is abruptly withdrawn are known as withdrawal syndrome and are often the only evidence of physical dependence.

dence, and withdrawal symptoms if the drug is stopped abruptly rather than gradually. For example, a hypertensive patient receiving a beta-adrenergic receptor blocker, such as propranolol, might have a good therapeutic response; but if the drug is stopped abruptly, there can be a withdrawal syndrome that consists of tachycardia and a rebound increase in blood pressure to a point that is temporarily higher than before administration of the medication began.

Because it is an illegal substance, some people consider any use of marijuana as substance abuse. However, this report uses the medical definition; that is, substance abuse is a maladaptive pattern of repeated substance use manifested by recurrent and significant adverse consequences.³ Substance abuse and dependence are both diagnoses of pathological substance use. Dependence is the more serious diagnosis and implies compulsive drug use that is difficult to stop despite significant substance-related problems (see Box 3.2).

Box 3.2

DSM-IV Criteria for Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

- (1) Tolerance, as defined by either of the following:
 - (a) A need for markedly increased amount of the substance to achieve intoxication or desired effect.
 - (b) Markedly diminished effect with continued use of the same amount of the substance.
- (2) Withdrawal, as defined by either of the following:
 - (a) The characteristic withdrawal syndrome for the substance.
 - (b) The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.
- (3) The substance is often taken in larger amounts or over a longer period than was intended.
- (4) There is a persistent desire or unsuccessful efforts to cut down or control substance use.
- (5) A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), to use the substance (e.g., chain-smoking), or to recover from its effects.
- (6) Important social, occupational, or recreational activities are given up or reduced because of substance use.
- (7) The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression or continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

Substance abuse with physiological dependence is diagnosed if there is evidence of tolerance or withdrawal.

Substance abuse without physiological dependence is diagnosed if there is no evidence of tolerance or withdrawal.

Reinforcement

Drugs vary in their ability to produce good feelings in users, and the more strongly reinforcing a drug is, the more likely it will be abused (G. Koob, Institute of Medicine (IOM) workshop). Marijuana is indisputably reinforcing for many people. The reinforcing properties of even so mild a

stimulant as caffeine are typical of reinforcement by addicting drugs (reviewed by Goldstein⁵⁴ in 1994). Caffeine is reinforcing for many people at low doses (100–200 mg, the average amount of caffeine in one to two cups of coffee) and is aversive at high doses (600 mg, the average amount of caffeine in six cups of coffee). The reinforcing effects of many drugs are different for different people. For example, caffeine was most reinforcing for test subjects who scored lowest on tests of anxiety but tended not to be reinforcing for the most anxious subjects.

As an argument to dispute the abuse potential of marijuana, some have cited the observation that animals do not willingly self-administer THC, as they will cocaine. Even if that were true, it would not be relevant to human use of marijuana. The value in animal models of drug self-administration is not that they are necessary to show that a drug is reinforcing but rather that they provide a model in which the effects of a drug can be studied. Furthermore, THC is indeed rewarding to animals at some doses but, like many reinforcing drugs, is aversive at high doses (4.0 mg/kg).⁹³ Similar effects have been found in experiments conducted in animals outfitted with intravenous catheters that allow them to self-administer WIN 55,212, a drug that mimics the effects of THC.¹⁰⁰

A specific set of neural pathways has been proposed to be a “reward system” that underlies the reinforcement of drugs of abuse and other pleasurable stimuli.⁵¹ Reinforcing properties of drugs are associated with their ability to increase concentrations of particular neurotransmitters in areas that are part of the proposed brain reward system. The median forebrain bundle and the nucleus accumbens are associated with brain reward pathways.⁸⁸ Cocaine, amphetamine, alcohol, opioids, nicotine, and THC¹⁴⁴ all increase extracellular fluid dopamine in the nucleus accumbens region (reviewed by Koob and Le Moal⁸⁸ and Nestler and Aghajanian¹¹⁰ in 1997). However, it is important to note that brain reward systems are not strictly “drug reinforcement centers.” Rather, their biological role is to respond to a range of positive stimuli, including sweet foods and sexual attraction.

Tolerance

The rate at which tolerance to the various effects of any drug develops is an important consideration for its safety and efficacy. For medical use, tolerance to some effects of cannabinoids might be desirable. Differences in the rates at which tolerance to the multiple effects of a drug develops can be dangerous. For example, tolerance to the euphoric effects of heroin develops faster than tolerance to its respiratory depressant effects, so heroin users tend to increase their daily doses to reach their desired level of euphoria, thereby putting themselves at risk for respiratory arrest. Because tolerance to the various effects of cannabinoids might

develop at different rates, it is important to evaluate independently their effects on mood, motor performance, memory, and attention, as well as any therapeutic use under investigation.

Tolerance to most of the effects of marijuana can develop rapidly after only a few doses, and it also disappears rapidly. Tolerance to large doses has been found to persist in experimental animals for long periods after cessation of drug use. Performance impairment is less among people who use marijuana heavily than it is among those who use marijuana only occasionally,^{29,104,124} possibly because of tolerance. Heavy users tend to reach higher plasma concentrations of THC than light users after similar doses of THC, arguing against the possibility that heavy users show less performance impairment because they somehow absorb less THC (perhaps due to differences in smoking behavior).⁹⁵

There appear to be variations in the development of tolerance to the different effects of marijuana and oral THC. For example, daily marijuana smokers participated in a residential laboratory study to compare the development of tolerance to THC pills and to smoked marijuana.^{61,62} One group was given marijuana cigarettes to smoke four times per day for four consecutive days; another group was given THC pills on the same schedule. During the four-day period, both groups became tolerant to feeling "high" and what they reported as a "good drug effect." In contrast, neither group became tolerant to the stimulatory effects of marijuana or THC on appetite. "Tolerance" does not mean that the drug no longer produced the effects but simply that the effects were less at the end than at the beginning of the four-day period. The marijuana smoking group reported feeling "mellow" after smoking and did not show tolerance to this effect; the group that took THC pills did not report feeling "mellow." The difference was also reported by many people who described their experiences to the IOM study team.

The oral and smoked doses were designed to deliver roughly equivalent amounts of THC to a subject. Each smoked marijuana dose consisted of five 10-second puffs of a marijuana cigarette containing 3.1% THC; the pills contained 30 mg of THC. Both groups also received placebo drugs during other four-day periods. Although the dosing of the two groups was comparable, different routes of administration resulted in different patterns of drug effect. The peak effect of smoked marijuana is usually felt within minutes and declines sharply after 30 minutes^{68,95}; the peak effect of oral THC is usually not felt until about an hour and lasts for several hours.¹¹⁸

Withdrawal

A distinctive marijuana and THC withdrawal syndrome has been

identified, but it is mild and subtle compared with the profound physical syndrome of alcohol or heroin withdrawal.^{31,74} The symptoms of marijuana withdrawal include restlessness, irritability, mild agitation, insomnia, sleep EEG disturbance, nausea, and cramping (Table 3.2). In addition to those symptoms, two recent studies noted several more. A group of adolescents under treatment for conduct disorders also reported fatigue and illusions or hallucinations after marijuana abstinence (this study is discussed further in the section on “Prevalence and Predictors of Dependence on Marijuana and Other Drugs”).³¹ In a residential study of daily

TABLE 3.2 Drug Withdrawal Symptoms

Nicotine	Alcohol	Marijuana	Cocaine	Opioids (e.g., heroin or morphine)
Restlessness Irritability Impatience, hostility Dysphoria Depression Anxiety Difficulty concentrating	Irritability Sleep disturbance Nausea	Restlessness Irritability Mild agitation Insomnia Sleep EEG disturbance Nausea Cramping	 Dysphoria Depression Sleepiness, fatigue Bradycardia	Restlessness Irritability Dysphoria Anxiety Insomnia Nausea Cramping
Decreased heart rate	Tachycardia, hypertension Sweating Seizures			Muscle aches Increased sensitivity to pain
Increased appetite or weight gain	Alcohol craving Delirium tremens ^a Tremor Perceptual distortion		Cocaine craving	Opioid craving

^aSevere agitation, confusion, visual hallucinations, fever, profuse sweating, nausea, diarrhea, dilated pupils.
SOURCE: O’Brien (1996).¹¹³

marijuana users, withdrawal symptoms included sweating and runny nose, in addition to those listed above.⁶² A marijuana withdrawal syndrome, however, has been reported only in a group of adolescents in treatment for substance abuse problems³¹ and in a research setting where subjects were given marijuana or THC daily.^{62,74}

Withdrawal symptoms have been observed in carefully controlled laboratory studies of people after use of both oral THC and smoked marijuana.^{61,62} In one study, subjects were given very high doses of oral THC: 180–210 mg per day for 10–20 days, roughly equivalent to smoking 9–10 2% THC cigarettes per day.⁷⁴ During the abstinence period at the end of the study, the study subjects were irritable and showed insomnia, runny nose, sweating, and decreased appetite. The withdrawal symptoms, however, were short lived. In four days they had abated. The time course contrasts with that in another study in which lower doses of oral THC were used (80–120 mg/day for four days) and withdrawal symptoms were still near maximal after four days.^{61,62}

In animals, simply discontinuing chronic heavy dosing of THC does not reveal withdrawal symptoms, but the “removal” of THC from the brain can be made abrupt by another drug that blocks THC at its receptor if administered when the chronic THC is withdrawn. The withdrawal syndrome is pronounced, and the behavior of the animals becomes hyperactive and disorganized.¹⁵³ The half-life of THC in brain is about an hour.^{16,24} Although traces of THC can remain in the brain for much longer periods, the amounts are not physiologically significant. Thus, the lack of a withdrawal syndrome when THC is abruptly withdrawn without administration of a receptor-blocking drug is probably not due to a prolonged decline in brain concentrations.

Craving

Craving, the intense desire for a drug, is the most difficult aspect of addiction to overcome. Research on craving has focused on nicotine, alcohol, cocaine, and opiates but has not specifically addressed marijuana.¹¹⁵ Thus, while this section briefly reviews what is known about drug craving, its relevance to marijuana use has not been established.

Most people who suffer from addiction relapse within a year of abstinence, and they often attribute their relapse to craving.⁵⁸ As addiction develops, craving increases even as maladaptive consequences accumulate. Animal studies indicate that the tendency to relapse is based on changes in brain function that continue for months or years after the last use of the drug.¹¹⁵ Whether neurobiological conditions change during the manifestation of an abstinence syndrome remains an unanswered question in drug abuse research.⁸⁸ The “liking” of sweet foods, for example, is

mediated by opioid forebrain systems and by brain stem systems, whereas “wanting” seems to be mediated by ascending dopamine neurons that project to the nucleus accumbens.¹⁰⁹

Anticraving medications have been developed for nicotine and alcohol. The antidepressant, bupropion, blocks nicotine craving, while naltrexone blocks alcohol craving.¹¹⁵ Another category of addiction medication includes drugs that block other drugs’ effects. Some of those drugs also block craving. For example, methadone blocks the euphoric effects of heroin and also reduces craving.

MARIJUANA USE AND DEPENDENCE

Prevalence of Use

Millions of Americans have tried marijuana, but most are not regular users. In 1996, 68.6 million people—32% of the U.S. population over 12 years old—had tried marijuana or hashish at least once in their lifetime, but only 5% were current users.¹³² Marijuana use is most prevalent among 18- to 25-year-olds and declines sharply after the age of 34 (Figure 3.1).^{77,132} Whites are more likely than blacks to use marijuana in adolescence, although the difference decreases by adulthood.¹³²

Most people who have used marijuana did so first during adolescence. Social influences, such as peer pressure and prevalence of use by peers, are highly predictive of initiation into marijuana use.⁹ Initiation is not, of course, synonymous with continued or regular use. A cohort of 456 students who experimented with marijuana during their high school years were surveyed about their reasons for initiating, continuing, and stopping their marijuana use.⁹ Students who began as heavy users were excluded from the analysis. Those who did not become regular marijuana users cited two types of reasons for discontinuing. The first was related to health and well-being; that is, they felt that marijuana was bad for their health or for their family and work relationships. The second type was based on age-related changes in circumstances, including increased responsibility and decreased regular contact with other marijuana users. Among high school students who quit, parental disapproval was a stronger influence than peer disapproval in discontinuing marijuana use. In the initiation of marijuana use, the reverse was true. The reasons cited by those who continued to use marijuana were to “get in a better mood or feel better.” Social factors were not a significant predictor of continued use. Data on young adults show similar trends. Those who use drugs in response to social influences are more likely to stop using them than those who also use them for psychological reasons.⁸⁰

The age distribution of marijuana users among the general popula-

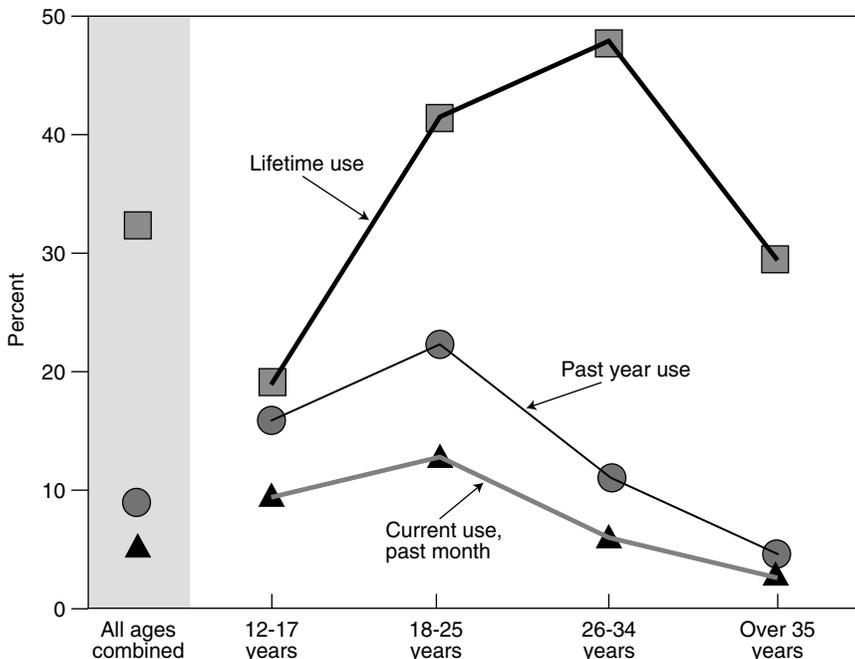


FIGURE 3.1 Age distribution of marijuana users among the general population.

tion contrasts with that of medical marijuana users. Marijuana use generally declines sharply after the age of 34 years, whereas medical marijuana users tend to be over 35. That raises the question of what, if any, relationship exists between abuse and medical use of marijuana; however, no studies reported in the scientific literature have addressed this question.

Prevalence and Predictors of Dependence on Marijuana and Other Drugs

Many factors influence the likelihood that a particular person will become a drug abuser or an addict; the user, the environment, and the drug are all important factors (Table 3.3).¹¹⁴ The first two categories apply to potential abuse of any substance; that is, people who are vulnerable to drug abuse for individual reasons and who find themselves in an environment that encourages drug abuse are initially likely to abuse the most readily available drug—regardless of its unique set of effects on the brain. The third category includes drug-specific effects that influence the abuse

TABLE 3.3 Factors That Are Correlated with Drug Dependence

Individual Factors

- Pharmacological effects of the drug
- Gender
- Age
- Genetic factors
- Individual risk-taking propensities
- Prior drug use

Environmental Factors

- Availability of the drug
- Acceptance of use of that drug in society
- Balance of social reinforcements and of punishments for use
- Balance of social reinforcements and of punishments for abstinence

SOURCE: Crowley and Rhine (1985).³²

liability of a particular drug. As discussed earlier in this chapter, the more strongly reinforcing a drug is, the more likely that it will be abused. The abuse liability of a drug is enhanced by how quickly its effects are felt, and this is determined by how the drug is delivered. In general, the effects of drugs that are inhaled or injected are felt within minutes, and the effects of drugs that are ingested take a half hour or more.

The proportion of people who become addicted varies among drugs. Table 3.4 shows estimates for the proportion of people among the general population who used or became dependent on different types of drugs. The proportion of users that ever became dependent includes anyone who was *ever* dependent—whether it was for a period of weeks or years—and thus includes more than those who are currently dependent. Compared to most other drugs listed in this table, dependence among marijuana users is relatively rare. This might be due to differences in specific drug effects, the availability of or penalties associated with the use of the different drugs, or some combination.

Daily use of most illicit drugs is extremely rare in the general population. In 1989, daily use of marijuana among high school seniors was less than that of alcohol (2.9% and 4.2%, respectively).⁷⁶

Drug dependence is more prevalent in some sectors of the population than in others. Age, gender, and race or ethnic group are all important.⁸ Excluding tobacco and alcohol, the following trends of drug dependence are statistically significant:⁸ Men are 1.6 times as likely than women to become drug dependent, non-Hispanic whites are about twice as likely as blacks to become drug dependent (the difference between non-Hispanic

TABLE 3.4 Prevalence of Drug Use and Dependence^a in the General Population

Drug Category	Proportion That Have Ever Used (%)	Proportion of Users That Ever Became Dependent (%)
Tobacco	76	32
Alcohol	92	15
Marijuana (including hashish)	46 ^b	9
Anxiolytics (including sedatives and hypnotic drugs)	13	9
Cocaine	16	17
Heroin	2	23

^aDiagnosis of drug dependence used in this study based on DSM-III-R criteria.²

^bThe percentage of people who ever used marijuana is higher than that reported by the National Household Survey on Drug Abuse (32%), probably due to different survey methods (for discussion, see Kandel, 1992⁷⁶).

SOURCE: Adapted from Table 2 in Anthony and co-workers (1994).⁸

and Hispanic whites was not significant), and people 25–44 years old are more than three times as likely as those over 45 years old to become drug dependent.

More often than not, drug dependence co-occurs with other psychiatric disorders. Most people with a diagnosis of drug dependence disorder also have a diagnosis of a another psychiatric disorder (76% of men and 65% of women).⁷⁶ The most frequent co-occurring disorder is alcohol abuse; 60% of men and 30% of women with a diagnosis of drug dependence also abuse alcohol. In women who are drug dependent, phobic disorders and major depression are almost equally common (29% and 28%, respectively). Note that this study distinguished only between alcohol, nicotine and “other drugs”; marijuana was grouped among “other drugs.” The frequency with which drug dependence and other psychiatric disorders co-occur might not be the same for marijuana and other drugs that were included in that category.

A strong association between drug dependence and antisocial personality or its precursor, conduct disorder, is also widely reported in children and adults (reviewed in 1998 by Robins¹²⁶). Although the causes of the association are uncertain, Robins recently concluded that it is more likely that conduct disorders generally lead to substance abuse than the reverse.¹²⁶ Such a trend might, however, depend on the age at which the conduct disorder is manifested.

A longitudinal study by Brooks and co-workers noted a significant relationship between adolescent drug use and disruptive disorders in young adulthood; except for earlier psychopathology, such as childhood conduct disorder, the drug use preceded the psychiatric disorders.¹⁸ In contrast with use of other illicit drugs and tobacco, moderate (less than once a week and more than once a month) to heavy marijuana use did not predict anxiety or depressive disorders; but it was similar to those other drugs in predicting antisocial personality disorder. The rates of disruptive disorders increased with increased drug use. Thus, heavy drug use among adolescents can be a warning sign for later psychiatric disorders; whether it is an early manifestation of or a cause of those disorders remains to be determined.

Psychiatric disorders are more prevalent among adolescents who use drugs—including alcohol and nicotine—than among those who do not.⁷⁹ Table 3.5 indicates that adolescent boys who smoke cigarettes daily are about 10 times as likely to have a psychiatric disorder diagnosis as those who do not smoke. However, the table does not compare intensity of use among the different drug classes. Thus, although *daily* cigarette smoking among adolescent boys is more strongly associated with psychiatric disorders than is any use of illicit substances, it does not follow that this comparison is true for every amount of cigarette smoking.⁷⁹

Few marijuana users become dependent on it (Table 3.4), but those who do encounter problems similar to those associated with dependence on other drugs.^{19,143} Dependence appears to be less severe among people

TABLE 3.5 Relative Prevalence of Diagnoses of Psychiatric Disorders Associated with Drug Use Among Children^a

Drug Use	Relative Prevalence Estimates ^b	
	Boys	Girls
Weekly alcohol use	6.1	1.6 (n.s.)
Daily cigarette smoking	9.8	2.1 (n.s.)
Any illicit substance use	3.2	5.3

^aSubjects were from 9 to 18 years old (average, 13 years old).

^bAn estimate of 1 means that the relative prevalence of the disorder is equal in those who do and those who do not use the particular type of drug; that is, there is no measurable association. An estimate greater than 1 indicates that the factor is associated. Substance abuse was excluded because the subjects were already grouped by high drug use. Except where noted (n.s.), all values are statistically significant.

SOURCE: Data from Table 4 in Kandel and co-workers (1997).⁷⁹

who use only marijuana than among those who abuse cocaine or those who abuse marijuana with other drugs (including alcohol).^{19,143}

Data gathered in 1990–1992 from the National Comorbidity Study of over 8,000 persons 15–54 years old indicate that 4.2% of the general population were dependent on marijuana at some time.⁸ Similar results for the frequency of substance abuse among the general population were obtained from the Epidemiological Catchment Area Program, a survey of over 19,000 people. According to data collected in the early 1980s for that study, 4.4% of adults have, at one time, met the criteria for marijuana dependence. In comparison, 13.8% of adults met the criteria for alcohol dependence and 36.0% for tobacco dependence. After alcohol and nicotine, marijuana was the substance most frequently associated with a diagnosis of substance dependence.

In a 15-year study begun in 1979, 7.3% of 1,201 adolescents and young adults in suburban New Jersey at some time met the criteria for marijuana dependence; this indicates that the rate of marijuana dependence might be even higher in some groups of adolescents and young adults than in the general population.⁷¹ Adolescents meet the criteria for drug dependence at lower rates of marijuana use than do adults, and this suggests that they are more vulnerable to dependence than adults²⁵ (see Box 3.2).

Youths who are already dependent on other substances are particularly vulnerable to marijuana dependence. For example, Crowley and co-workers³¹ interviewed a group of 229 adolescent patients in a residential treatment program for delinquent, substance-involved youth and found that those patients were dependent on an average of 3.2 substances. The adolescents had previously been diagnosed as dependent on at least one substance (including nicotine and alcohol) and had three or more conduct disorder symptoms during their life. About 83% of those who had used marijuana at least six times went on to develop marijuana dependence. About equal numbers of youths in the study had a diagnosis of marijuana dependence and a diagnosis of alcohol dependence; fewer were nicotine dependent. Comparisons of dependence potential between different drugs should be made cautiously. The probability that a particular drug will be abused is influenced by many factors, including the specific drug effects and availability of the drug.

Although parents often state that marijuana caused their children to be rebellious, the troubled adolescents in the study by Crowley and co-workers developed conduct disorders *before* marijuana abuse. That is consistent with reports that the more symptoms of conduct disorders children have, the younger they begin drug abuse,¹²⁷ and that the earlier they begin drug use, the more likely it is to be followed by abuse or dependence.¹²⁵

Genetic factors are known to play a role in the likelihood of abuse for

drugs other than marijuana,^{7,129} and it is not unexpected that genetic factors play a role in the marijuana experience, including the likelihood of abuse. A study of over 8,000 male twins listed in the Vietnam Era Twin Registry indicated that genes have a statistically significant influence on whether a person finds the effects of marijuana pleasant.⁹⁷ Not surprisingly, people who found marijuana to be pleasurable used it more often than those who found it unpleasant. The study suggested that, although social influences play an important role in the initiation of use, individual differences—perhaps associated with the brain’s reward system—influence whether a person will continue using marijuana. Similar results were found in a study of female twins.⁸⁶ Family and social environment strongly influenced the likelihood of ever using marijuana but had little effect on the likelihood of heavy use or abuse. The latter were more influenced by genetic factors. Those results are consistent with the finding that the degree to which rats find THC rewarding is genetically based.⁹²

In summary, although few marijuana users develop dependence, some do. But they appear to be less likely to do so than users of other drugs (including alcohol and nicotine), and marijuana dependence appears to be less severe than dependence on other drugs. Drug dependence is more prevalent in some sectors of the population than others, but no group has been identified as particularly vulnerable to the drug-specific effects of marijuana. Adolescents, especially troubled ones, and people with psychiatric disorders (including substance abuse) appear to be more likely than the general population to become dependent on marijuana.

If marijuana or cannabinoid drugs were approved for therapeutic uses, it would be important to consider the possibility of dependence, particularly for patients at high risk for substance dependence. Some controlled substances that are approved medications produce dependence after long-term use; this, however, is a normal part of patient management and does not generally present undue risk to the patient.

Progression from Marijuana to Other Drugs

The fear that marijuana use might cause, as opposed to merely precede, the use of drugs that are more harmful is of great concern. To judge from comments submitted to the IOM study team, it appears to be of greater concern than the harms directly related to marijuana itself. The discussion that marijuana is a “gateway” drug implicitly recognizes that other illicit drugs might inflict greater damage to health or social relations than marijuana. Although the scientific literature generally discusses drug use progression between a variety of drug classes, including alcohol and tobacco, the public discussion has focused on marijuana as a “gateway”

drug that leads to abuse of more harmful illicit drugs, such as cocaine and heroin.

There are strikingly regular patterns in the progression of drug use from adolescence to adulthood. Because it is the most widely used illicit drug, marijuana is predictably the first illicit drug that most people encounter. Not surprisingly, most users of other illicit drugs used marijuana first.^{81,82} In fact, most drug users do not begin their drug use with marijuana—they begin with alcohol and nicotine, usually when they are too young to do so legally.^{82,90}

The gateway analogy evokes two ideas that are often confused. The first, more often referred to as the “stepping stone” hypothesis, is the idea that progression from marijuana to other drugs arises from pharmacological properties of marijuana itself.⁸² The second is that marijuana serves as a gateway to the world of illegal drugs in which youths have greater opportunity and are under greater social pressure to try other illegal drugs. The latter interpretation is most often used in the scientific literature, and it is supported, although not proven, by the available data.

The stepping stone hypothesis applies to marijuana only in the broadest sense. People who enjoy the effects of marijuana are, logically, more likely to be willing to try other mood-altering drugs than are people who are not willing to try marijuana or who dislike its effects. In other words, many of the factors associated with a willingness to use marijuana are, presumably, the same as those associated with a willingness to use other illicit drugs. Those factors include physiological reactions to the drug effect, which are consistent with the stepping stone hypothesis, but also psychosocial factors, which are independent of drug-specific effects. There is no evidence that marijuana serves as a stepping stone on the basis of its particular physiological effect. One might argue that marijuana is generally used before other illicit mood-altering drugs, in part, because its effects are milder; in that case, marijuana is a stepping stone only in the same sense as taking a small dose of a particular drug and then increasing that dose over time is a stepping stone to increased drug use.

Whereas the stepping stone hypothesis presumes a predominantly physiological component of drug progression, the gateway theory is a social theory. The latter does not suggest that the pharmacological qualities of marijuana make it a risk factor for progression to other drug use. Instead, the legal status of marijuana makes it a gateway drug.⁸²

Psychiatric disorders are associated with substance dependence and are probably risk factors for progression in drug use. For example, the troubled adolescents studied by Crowley and co-workers³¹ were dependent on an average of 3.2 substances, and this suggests that their conduct disorders were associated with increased risk of progressing from one drug to another. Abuse of a single substance is probably also a risk factor

for later multiple drug use. For example, in a longitudinal study that examined drug use and dependence, about 26% of problem drinkers reported that they first used marijuana after the onset of alcohol-related problems (R. Pandina, IOM workshop). The study also found that 11% of marijuana users developed chronic marijuana problems; most also had alcohol problems.

Intensity of drug use is an important risk factor in progression. Daily marijuana users are more likely than their peers to be extensive users of other substances (for review, see Kandel and Davies⁷⁸). Of 34- to 35-year-old men who had used marijuana 10–99 times by the age 24–25, 75% never used any other illicit drug; 53% of those who had used it more than 100 times did progress to using other illicit drugs 10 or more times.⁷⁸ Comparable proportions for women are 64% and 50%.

The factors that best predict use of illicit drugs other than marijuana are probably the following: age of first alcohol or nicotine use, heavy marijuana use, and psychiatric disorders. However, progression to illicit drug use is not synonymous with heavy or persistent drug use. Indeed, although the age of onset of use of licit drugs (alcohol and nicotine) predicts later illicit drug use, it does *not* appear to predict persistent or heavy use of illicit drugs.⁹⁰

Data on the gateway phenomenon are often overinterpreted. For example, one study reports that “marijuana’s role as a gateway drug appears to have increased.”⁵⁵ It was a retrospective study based on interviews of drug abusers who reported smoking crack or injecting heroin daily. The data from the study provide no indication of what proportion of marijuana users become serious drug abusers; rather, they indicate that serious drug abusers usually use marijuana before they smoke crack or inject heroin. Only a small percentage of the adult population uses crack or heroin daily; during the five-year period from 1993 to 1997, an average of three people per 1,000 used crack and about two per 1,000 used heroin in the preceding month.¹³²

Many of the data on which the gateway theory is based do not measure dependence; instead, they measure use—even once-only use. Thus, they show only that marijuana users are more likely to use other illicit drugs (even if only once) than are people who never use marijuana, not that they become dependent or even frequent users. The authors of these studies are careful to point out that their data should not be used as evidence of an inexorable *causal* progression; rather they note that identifying stage-based user groups makes it possible to identify the specific risk factors that predict movement from one stage of drug use to the next—the real issue in the gateway discussion.²⁵

In the sense that marijuana use typically precedes rather than follows initiation into the use of other illicit drugs, it is indeed a gateway drug.

However, it does not appear to be a gateway drug to the extent that it is the *cause* or even that it is the most significant predictor of serious drug abuse; that is, care must be taken not to attribute cause to association. The most consistent predictors of serious drug use appear to be the intensity of marijuana use and co-occurring psychiatric disorders or a family history of psychopathology (including alcoholism).^{78,83}

An important caution is that data on drug use progression pertain to *nonmedical* drug use. It does not follow from those data that if marijuana were available by prescription for *medical* use, the pattern of drug use would be the same. Kandel and co-workers also included nonmedical use of prescription psychoactive drugs in their study of drug use progression.⁸² In contrast with the use of alcohol, nicotine, and illicit drugs, there was not a clear and consistent sequence of drug use involving the abuse of prescription psychoactive drugs. The current data on drug use progression neither support nor refute the suggestion that medical availability would increase drug abuse among medical marijuana users. Whether the medical use of marijuana might encourage drug abuse among the general community—not among medical marijuana users themselves but among others simply because of the fact that marijuana would be used for medical purposes—is another question.

LINK BETWEEN MEDICAL USE AND DRUG ABUSE

Almost everyone who spoke or wrote to the IOM study team about the potential harms posed by the medical use of marijuana felt that it would send the wrong message to children and teenagers. They stated that information about the harms caused by marijuana is undermined by claims that marijuana might have medical value. Yet many of our powerful medicines are also dangerous medicines. These two facets of medicine—effectiveness and risk—are inextricably linked.

The question here is not whether marijuana can be both harmful and helpful but whether the perception of its benefits will increase its abuse. For now any answer to the question remains conjecture. Because marijuana is not an approved medicine, there is little information about the consequences of its medical use in modern society. Reasonable inferences might be drawn from some examples. Opiates, such as morphine and codeine, are an example of a class of drugs that is both abused to great harm and used to great medical benefit, and it would be useful to examine the relationship between their medical use and their abuse. In a “natural experiment” during 1973–1978 some states decriminalized marijuana, and others did not. Finally, one can examine the short-term consequences of the publicity surrounding the 1996 medical marijuana campaign in California and ask whether it had any measurable impact on marijuana con-

sumption among youth in California; the consequences of “message” that marijuana might have medical use are examined below.

Medical Use and Abuse of Opiates

Two highly influential papers published in the 1920s and 1950s led to widespread concern among physicians and medical licensing boards that liberal use of opiates would result in many addicts (reviewed by Moulin and co-workers¹⁰⁶ in 1996). Such fears have proven unfounded; it is now recognized that fear of producing addicts through medical treatment resulted in needless suffering among patients with pain as physicians needlessly limited appropriate doses of medications.^{27,44} Few people begin their drug addiction problems with misuse of drugs that have been prescribed for medical use.¹¹⁴ Opiates are carefully regulated in the medical setting, and diversion of medically prescribed opiates to the black market is not generally considered to be a major problem.

No evidence suggests that the use of opiates or cocaine for medical purposes has increased the perception that their illicit use is safe or acceptable. Clearly, there are risks that patients will abuse marijuana for its psychoactive effects and some likelihood of diversion of marijuana from legitimate medical channels into the illicit market. But those risks do not differentiate marijuana from many accepted medications that are abused by some patients or diverted from medical channels for non-medical use. Medications with abuse potential are placed in Schedule II of the Controlled Substances Act, which brings them under stricter control, including quotas on the amount that can be legally manufactured (see chapter 5 for discussion of the Controlled Substances Act). That scheduling also signals to physicians that a drug has abuse potential and that they should monitor its use by patients who could be at risk for drug abuse.

Marijuana Decriminalization

Monitoring the Future, the annual survey of values and lifestyles of high school seniors, revealed that high school seniors in decriminalized states reported using no more marijuana than did their counterparts in states where marijuana was not decriminalized.⁷² Another study reported somewhat conflicting evidence indicating that decriminalization had increased marijuana use.¹⁰⁵ That study used data from the Drug Awareness Warning Network (DAWN), which has collected data on drug-related emergency room (ER) cases since 1975. There was a greater increase from 1975 to 1978 in the proportion of ER patients who had used marijuana in states that had decriminalized marijuana in 1975–1976 than in states that had not decriminalized it (Table 3.6). Despite the greater

TABLE 3.6 Effect of Decriminalization on Marijuana Use in Emergency Room (ER) Cases

		Total Reports of Drug Use per ER ^a	
		States That Decriminalized Marijuana	States That Did Not Decriminalize Marijuana
Period ^b			
Marijuana use	1975	0.8	1.5
	1978	2.7	2.5
Other drug use	1975	47	55
	1978	55	70

^aData are based on patient self-reports.

^bStates that decriminalized marijuana did so after 1975 and before 1978. The 1975 values reflect ER marijuana reports before or in the first months of decriminalization, whereas 1978 values reflect ER reports when decriminalization laws had been in effect at least a year. The 1978 levels are median values for quarters in 1978 and are derived from Figures 1 and 2 in Model (1993).¹⁰⁵

SOURCE: Adapted from Figures 1 and 2 in Model (1993).¹⁰⁵

increase among decriminalized states, the proportion of marijuana users among ER patients by 1978 was about equal in states that had and states that had not decriminalized marijuana. That is because the non-decriminalized states had higher rates of marijuana use *before* decriminalization. In contrast with marijuana use, rates of other illicit drug use among ER patients were substantially higher in states that did not decriminalize marijuana use. Thus, there are different possible reasons for the greater increase in marijuana use in the decriminalized states. On the one hand, decriminalization might have led to an increased use of marijuana (at least among people who sought health care in hospital ERs). On the other hand, the lack of decriminalization might have encouraged greater use of drugs that are even more dangerous than marijuana.

The differences between the results for high school seniors from the Monitoring the Future study and the DAWN data are unclear, although the author of the latter study suggests that the reasons might lie in limitations inherent in how the DAWN data are collected.¹⁰⁵

In 1976, the Netherlands adopted a policy of toleration for possession of up to 30 g of marijuana. There was little change in marijuana use during the seven years after the policy change, which suggests that the change itself had little effect; however, in 1984, when Dutch “coffee shops” that sold marijuana commercially spread throughout Amsterdam, marijuana

use began to increase.⁹⁸ During the 1990s, marijuana use has continued to increase in the Netherlands at the same rate as in the United States and Norway—two countries that strictly forbid marijuana sale and possession. Furthermore, during this period, approximately equal percentages of American and Dutch 18 year olds used marijuana; Norwegian 18 year olds were about half as likely to have used marijuana. The authors of this study conclude that there is little evidence that the Dutch marijuana depenalization policy led to increased marijuana use, although they note that commercialization of marijuana might have contributed to its increased use. Thus, there is little evidence that decriminalization of marijuana use necessarily leads to a substantial increase in marijuana use.

The Medical Marijuana Debate

The most recent National Household Survey on Drug Abuse showed that among people 12–17 years old the perceived risk associated with smoking marijuana once or twice a week had decreased significantly between 1996 and 1997.¹³² (Perceived risk is measured as the percentage of survey respondents who report that they “perceive great risk of harm” in using a drug at a specified frequency.) At first glance, that might seem to validate the fear that the medical marijuana debate of 1996—before passage of the California medical marijuana referendum in November 1997—had sent a message that marijuana use is safe. But a closer analysis of the data shows that Californian youth were an exception to the national trend. In contrast to the national trend, the perceived risk of marijuana use did not change among California youth between 1996 and 1997.^{132*} In summary, there is no evidence that the medical marijuana debate has altered adolescents’ perceptions of the risks associated with marijuana use.¹³²

PSYCHOLOGICAL HARMS

In assessing the relative risks and benefits related to the medical use of marijuana, the psychological effects of marijuana can be viewed both as unwanted side effects and as potentially desirable end points in medical treatment. However, the vast majority of research on the psychological effects of marijuana has been in the context of assessing the drug’s intoxicating effects when it is used for nonmedical purposes. Thus, the litera-

*Although Arizona also passed a medical marijuana referendum, it was embedded in a broader referendum concerning prison sentencing. Hence, the debate in Arizona did not focus on medical marijuana the way it did in California, and changes in Arizona youths’ attitudes likely reflect factors peripheral to medical marijuana.

ture does not directly address the effects of marijuana taken for medical purposes.

There are some important caveats to consider in attempting to extrapolate from the research mentioned above to the medical use of marijuana. The circumstances under which psychoactive drugs are taken are an important influence on their psychological effects. Furthermore, research protocols to study marijuana's psychological effects in most instances were required to use participants who already had experience with marijuana. People who might have had adverse reactions to marijuana either would choose not to participate in this type of study or would be screened out by the investigator. Therefore, the incidence of adverse reactions to marijuana that might occur in people with no marijuana experience cannot be estimated from such studies. A further complicating factor concerns the dose regimen used for laboratory studies. In most instances, laboratory research studies have looked at the effects of single doses of marijuana, which might be different from those observed when the drug is taken repeatedly for a chronic medical condition.

Nonetheless, laboratory studies are useful in suggesting what psychological functions might be studied when marijuana is evaluated for medical purposes. Results of laboratory studies indicate that acute and chronic marijuana use has pronounced effects on mood, psychomotor, and cognitive functions. These psychological domains should therefore be considered in assessing the relative risks and therapeutic benefits related to marijuana or cannabinoids for any medical condition.

Psychiatric Disorders

A major question remains as to whether marijuana can produce lasting mood disorders or psychotic disorders, such as schizophrenia. Georgotas and Zeidenberg⁵² reported that smoking 10–22 marijuana cigarettes per day was associated with a gradual waning of the positive mood and social facilitating effects of marijuana and an increase in irritability, social isolation, and paranoid thinking. Inasmuch as smoking *one* cigarette is enough to make a person feel “high” for about 1–3 hours,^{68,95,118} the subjects in that study were taking very high doses of marijuana. Reports have described the development of apathy, lowered motivation, and impaired educational performance in heavy marijuana users who do not appear to be behaviorally impaired in other ways.^{121,122} There are clinical reports of marijuana-induced psychosis-like states (schizophrenia-like, depression, and/or mania) lasting for a week or more.¹¹² Hollister suggests that, because of the varied nature of the psychotic states induced by marijuana, there is no specific “marijuana psychosis.” Rather, the marijuana experience might trigger latent psychopathology of many types.⁶⁶

More recently, Hall and colleagues⁶⁰ concluded that “there is reasonable evidence that heavy cannabis use, and perhaps acute use in sensitive individuals, can produce an acute psychosis in which confusion, amnesia, delusions, hallucinations, anxiety, agitation and hypomanic symptoms predominate.” Regardless of which of those interpretations is correct, the two reports agree that there is little evidence that marijuana alone produces a psychosis that persists after the period of intoxication.

Schizophrenia

The association between marijuana and schizophrenia is not well understood. The scientific literature indicates general agreement that heavy marijuana use can precipitate schizophrenic episodes but not that marijuana use can cause the underlying psychotic disorder.^{59,96,151} As noted earlier, drug abuse is common among people with psychiatric disorders. Estimates of the prevalence of marijuana use among schizophrenics vary considerably but are in general agreement that it is at least as great as that among the general population.¹³⁴ Schizophrenics prefer the effects of marijuana to those of alcohol and cocaine,³⁵ which they seem to use less often than does the general population.¹³⁴ The reasons for this are unknown, but it raises the possibility that schizophrenics might obtain some symptomatic relief from moderate marijuana use. But overall, compared with the general population, people with schizophrenia or with a family history of schizophrenia are likely to be at greater risk for adverse psychiatric effects from the use of cannabinoids.

Cognition

As discussed earlier, acutely administered marijuana impairs cognition.^{60,66,112} Positron emission tomography (PET) imaging allows investigators to measure the acute effects of marijuana smoking on active brain function. Human volunteers who perform auditory attention tasks before and after smoking a marijuana cigarette show impaired performance while under the influence of marijuana; this is associated with substantial reduction in blood flow to the temporal lobe of the brain, an area that is sensitive to such tasks.^{116,117} Marijuana smoking increases blood flow in other brain regions, such as the frontal lobes and lateral cerebellum.^{101,155} Earlier studies purporting to show structural changes in the brains of heavy marijuana users²² have not been replicated with more sophisticated techniques.^{28,89}

Nevertheless, recent studies^{14,122} have found subtle defects in cognitive tasks in heavy marijuana users after a brief period (19–24 hours) of marijuana abstinence. Longer term cognitive deficits in heavy marijuana

users have also been reported.¹⁴⁰ Although these studies have attempted to match heavy marijuana users with subjects of similar cognitive abilities before exposure to marijuana use, the adequacy of this matching has been questioned.¹³³ The complex methodological issues facing research in this area are well reviewed in an article by Pope and colleagues.¹²¹ Care must be exercised so that studies are designed to differentiate between changes in brain function caused the effects of marijuana and by the illness for which marijuana is being given. AIDS dementia is an obvious example of this possible confusion. It is also important to determine whether repeated use of marijuana at therapeutic dosages produces any irreversible cognitive effects.

Psychomotor Performance

Marijuana administration has been reported to affect psychomotor performance on a number of tasks. The review by Chait and Pierri²³ not only details the studies that have been done but also points out the inconsistencies among studies, the methodological shortcomings of many studies, and the large individual differences among the studies attributable to subject, situational, and methodological factors. Those factors must be considered in studies of psychomotor performance when participants are involved in a clinical trial of the efficacy of marijuana. The types of psychomotor functions that have been shown to be disrupted by the acute administration of marijuana include body sway, hand steadiness, rotary pursuit, driving and flying simulation, divided attention, sustained attention, and the digit-symbol substitution test. A study of experienced airplane pilots showed that even 24 hours after a single marijuana cigarette their performance on flight simulator tests was impaired.¹⁶³ Before the tests, however, they told the study investigators that they were sure their performance would be unaffected.

Cognitive impairments associated with acutely administered marijuana limit the activities that people would be able to do safely or productively. For example, no one under the influence of marijuana or THC should drive a vehicle or operate potentially dangerous equipment.

Amotivational Syndrome

One of the more controversial effects claimed for marijuana is the production of an "amotivational syndrome." This syndrome is not a medical diagnosis, but it has been used to describe young people who drop out of social activities and show little interest in school, work, or other goal-directed activity. When heavy marijuana use accompanies these symptoms, the drug is often cited as the cause, but no convincing data demon-

strate a causal relationship between marijuana smoking and these behavioral characteristics.²³ It is not enough to observe that a chronic marijuana user lacks motivation. Instead, relevant personality traits and behavior of subjects must be assessed before and after the subject becomes a heavy marijuana user. Because such research can only be done on subjects who become heavy marijuana users on their own, a large population study—such as the Epidemiological Catchment Area study described earlier in this chapter—would be needed to shed light on the relationship between motivation and marijuana use. Even then, although a causal relationship between the two could, in theory, be dismissed by an epidemiological study, causality could not be proven.

Summary

Measures of mood, cognition, and psychomotor performance should be incorporated into clinical trials evaluating the efficacy of marijuana or cannabinoid drugs for a given medical condition. Ideally, participants would complete mood assessment questionnaires at various intervals throughout the day for a period before; every week during; and, where appropriate, after marijuana therapy. A full psychological screening of research participants should be conducted to determine whether there is an interaction between the mood-altering effects of chronic marijuana use and the psychological characteristics of the subjects. Similarly, the cognitive and psychomotor functioning should be assessed before and regularly during the course of a chronic regimen of marijuana or cannabinoid treatment to determine the extent to which tolerance to the impairing effects of marijuana develops and to monitor whether new problems develop.

When compared with changes produced by either placebo or an active control medication, the magnitude of desirable therapeutic effects and the frequency and magnitude of adverse psychological side effects of marijuana could be determined. That would allow a more thorough assessment of the risk:benefit ratio associated with the use of marijuana for a given indication.

CONCLUSION: The psychological effects of cannabinoids, such as anxiety reduction, sedation, and euphoria, can influence their potential therapeutic value. Those effects are potentially undesirable in some patients and situations and beneficial in others. In addition, psychological effects can complicate the interpretation of other aspects of the drug's effect.

RECOMMENDATION: Psychological effects of cannabinoids, such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.

PHYSIOLOGICAL HARMS: TISSUE AND ORGAN DAMAGE

Many people who spoke to the IOM study team in favor of the medical use of marijuana cited the absence of marijuana overdoses as evidence that it is safe. Indeed, epidemiological data indicate that in the general population marijuana use is not associated with increased mortality.¹³⁸ However, other serious health outcomes should be considered, and they are discussed below.

It is important to keep in mind that most of the studies that report physiological harm resulting from marijuana use are based on the effects of marijuana smoking. Thus, we emphasize that the effects reported cannot be presumed to be caused by THC alone or even in combination with other cannabinoids found in marijuana. It is likely that smoke is a major cause of the reported effects. In most studies the methods used make it impossible to weigh the relative contributions of smoke versus cannabinoids.

Immune System

The relationship between marijuana and the immune system presents many facets, including potential benefits and suspected harms. This section reviews the evidence on suspected harms to the immune system caused by marijuana use.

Despite the many claims that marijuana suppresses the human immune system, the health effects of marijuana-induced immunomodulation are still unclear. Few studies have been done with animals or humans to assess the effects of marijuana exposure on host resistance to bacteria, viruses, or tumors.

Human Studies

Several approaches have been used to determine the effects of marijuana on the human immune system. Each has serious limitations, which are discussed below.

Assays of Leukocytes from Marijuana Smokers. One of the more common approaches has been to isolate peripheral blood leukocytes from people who have smoked marijuana in order to evaluate the immune

response of those cells *in vitro*—most often by measuring mitogen-induced cell proliferation, a normal immune response. Almost without exception, this approach has failed to demonstrate any reduction in leukocyte function. The major problem with the approach is that after blood samples are drawn from the study subjects the leukocytes must be isolated from whole blood before they are tested. That is done by high-speed centrifugation followed by extensive washing of the cells, which removes the cannabinoid; perhaps for this reason no adverse effects have been demonstrated in peripheral blood leukocytes from marijuana smokers.^{75,91,123,160}

Leukocyte Responses to THC. Another approach is to isolate peripheral blood leukocytes from healthy control subjects who do not smoke marijuana and then to measure the effect of THC on the ability of these cells to proliferate in response to mitogenic stimulation *in vitro*. One important difference between leukocytes isolated from a marijuana smoker, as described above, and leukocyte cell cultures to which THC has been added directly is in the cannabinoid composition. Marijuana smoke contains many distinct cannabinoid compounds of which THC is just one. Moreover, the immunomodulatory activity of many of the other cannabinoid compounds has never been tested, and it is now known that at least one of those—cannabinol (CBN)—has greater activity on the immune system than on the central nervous system,⁶⁴ so it is unclear whether the profile of activity observed with THC accurately represents the effects of marijuana smoke on immune competence. Likewise, the extent to which different cannabinoids in combination exhibit additive, synergistic, or antagonistic effects with respect to immunomodulatory activity is unclear. The issue is complicated by the fact that leukocytes express both types of cannabinoid receptors: CB₁ and CB₂.

An additional factor that might affect the immunomodulatory activity of cannabinoids in leukocytes is metabolism. Leukocytes have very low levels of the cytochrome P-450 drug-metabolizing enzymes,²⁰ so the metabolism of cannabinoids is probably different between *in vivo* and *in vitro* exposure. That last point is pertinent primarily to investigations of chronic, not acute, cannabinoid exposure.

Human-Derived Cell Lines. A third approach for investigating the effects of cannabinoids on human leukocytes has been to study human-derived cell lines.* As described above, the cell lines are treated *in vitro* with cannabinoids to test their responses to different stimuli. Although cell lines

*Cell lines are created by removing cells from an organism and then treating them so they are “immortalized,” meaning they will continue to divide and multiply indefinitely in culture. Cellular processes can then be studied in isolation from their original source.

are a convenient source of human cells, the problems described above apply here as well. In addition, the cell lines might not be the same as the original cells. For example, cell lines do not necessarily have the same number of cannabinoid receptors as the original human cells.

Rodent Studies

The most widely used approach is to evaluate the effects of cannabinoids in rodents, using rodent-derived cells *in vitro*. The rationale is that the human and rodent immune systems are remarkably similar, and it is assumed that the effects produced by cannabinoids on the rodent immune system will be similar to those produced in humans. Although no substantial species differences in immune system sensitivity to cannabinoids have been reported, the possibility should be considered.

Summary

The complete effect of marijuana smoking on immune function remains unknown. More important, it is not known whether smoking leads to increased rates of infections, tumors, allergies, or autoimmune responses. The problem is how to duplicate the “normal” marijuana smoking pattern while removing other potential immunomodulating lifestyle factors, such as alcohol and tobacco use. Epidemiological studies are needed to determine whether marijuana users have a higher incidence of such diseases, as infections, tumors, allergies, and autoimmune diseases. Studies on resistance to bacterial and viral infection are clearly needed and should involve the collaboration of immunologists, infectious disease specialists, oncologists, and pharmacologists.

Marijuana Smoke

Tobacco is the predominant cause of such lung diseases as cancer and emphysema, and marijuana smoke contains many of the components of tobacco smoke.⁶⁹ Thus, it is important to consider the relationship between habitual marijuana smoking and some lung diseases.

Given a cigarette of comparable weight, as much as four times the amount of tar can be deposited in the lungs of marijuana smokers as in the lungs of tobacco smokers.¹⁶² The difference is due primarily to the differences in filtration and smoking technique between tobacco and marijuana smokers. Marijuana cigarettes usually do not have filters, and marijuana smokers typically develop a larger puff volume, inhale more deeply, and hold their breath several times longer than tobacco smokers.¹¹⁹ However, a marijuana cigarette smoked recreationally typically is not packed

as tightly as a tobacco cigarette, and the smokable substance is about half that in a tobacco cigarette. In addition, tobacco smokers generally smoke considerably more cigarettes per day than do marijuana smokers.

Cellular Damage

Lymphocytes: T and B Cells. Human studies of the effect of marijuana smoking on immune cell function are not all consistent with cannabinoid cell culture and animal studies. For example, antibody production was decreased in a group of hospitalized patients who smoked marijuana for four days (12 cigarettes/day), but the decrease was seen in only one subtype of humoral antibody (IgG), whereas two other subtypes (IgA and IgM) remained normal and one (IgE) was increased.¹⁰⁸ In addition, T cell proliferation was normal in the blood of a group of marijuana smokers, although closer evaluation showed an increase in one subset of T cells¹⁶¹ and a decrease in a different subset (CD8).¹⁵⁷ It appears that marijuana use is associated with intermittent disturbances in T and B cell function, but the magnitude is small and other measures are often normal.⁸⁷

Macrophages. Alveolar macrophages are the principal immune-effector cells in the lung and are primarily responsible for protecting the lung against infectious microorganisms, inhaled foreign substances, and tumor cells. They are increased during tissue inflammation. In a large sample of volunteers, habitual marijuana smokers had twice as many alveolar macrophages as nonsmokers, and smokers of both marijuana and tobacco had twice as many again.¹¹ Marijuana smoking also reduced the ability of alveolar macrophages to kill fungi, such as *Candida albicans*;^{*} pathogenic bacteria, such as *Staphylococcus aureus*; and tumor target cells. The reduction in ability to destroy fungal organisms was similar to that seen in tobacco smokers. The inability to kill pathogenic bacteria was not seen in tobacco smokers.¹⁰ Furthermore, marijuana smoking depressed production of proinflammatory cytokines, such as TNF-I and IL-6, but not of immunosuppressive cytokines.¹⁰ Cytokines are important regulators of macrophage function, so this marijuana-related decrease in inflammatory cytokine production might be a mechanism whereby marijuana smokers are less able to destroy fungal and bacterial organisms, as well as tumor cells.

The inability of alveolar macrophages from habitual marijuana smokers without apparent disease to destroy fungi, bacteria, and tumor cells

^{*}*Candida albicans* is a yeast infection that is particularly prevalent among people whose immune systems are suppressed, such as in AIDS patients.

and to release proinflammatory cytokines, suggests that marijuana might be an immunosuppressant with clinically significant effects on host defense. Therefore, the risks of smoking marijuana should be seriously weighed before recommending its use in any patient with preexisting immune deficits—including AIDS patients, cancer patients, and those receiving immunosuppressive therapies (for example, transplant or cancer patients).

Bronchial and Pulmonary Damage

Animal Studies. A number of animal studies have revealed respiratory tract changes and diseases associated with marijuana smoking, but others have not. Extensive damage to the smaller airways, which are the major site of chronic obstructive pulmonary disease (COPD),* and acute and chronic pneumonia have been observed in various species exposed to different doses of marijuana smoke.^{41,42,128} In contrast, rats exposed to increasing doses of marijuana smoke for one year did not show any signs of COPD, whereas rats exposed to tobacco smoke did.⁶⁷

Chronic Bronchitis and Respiratory Illness. Results of human studies suggest that there is a greater chance of respiratory illness in people who smoke marijuana. In a survey of outpatient medical visits at a large health maintenance organization (HMO), marijuana users were more likely to seek help for respiratory illnesses than people who smoked neither marijuana or tobacco.¹²⁰ However, the incidence of seeking help for respiratory illnesses was not higher in those who smoked marijuana for 10 years or more than in those who smoked for less than 10 years. One explanation for this is that people who experience respiratory symptoms are more likely to quit smoking and that people who continue to smoke constitute a set of survivors who do not develop or are indifferent to such symptoms. One limitation of this study is that no data were available on the use of cocaine, which when used with marijuana could contribute to the observed differences. Another limitation is that the survey relied on self-reporting; tobacco, alcohol, and marijuana use might have been underreported (S. Sidney, IOM workshop).

When marijuana smokers were compared with nonsmokers and tobacco smokers in a group of 446 volunteers, 15–20% of the marijuana smokers reported symptoms of chronic bronchitis, including chronic

*COPD is a slow progressive obstruction of the airways, loss of their elasticity, and loss of lung volume, characterized by chronic shortness of breath, chronic bronchitis, and reduced oxygenation of blood.

cough and phlegm production,¹⁴⁶ and 20–25% of the tobacco smokers reported symptoms of chronic bronchitis. Despite a marked disparity in the amount of each substance smoked per day (three or four joints of marijuana versus more than 20 cigarettes of tobacco), the difference in the percentages of tobacco smokers and marijuana smokers experiencing symptoms of chronic bronchitis was statistically insignificant.¹⁴⁶ Similar findings were reported by Bloom and co-workers,¹⁵ who noted an additive effect of smoking both marijuana and tobacco.

Bronchial Tissue Changes. Habitual marijuana smoking is associated with changes in the lining of the human respiratory tract. Many marijuana or tobacco smokers have increased redness (erythema) and swelling (edema) of the airway tissues and increased mucous secretions.^{43,56} In marijuana smokers the number and size of small blood vessels in the bronchial wall are increased, tissue edema is present, and the normal ciliated cells* lining the inner surface of the bronchial wall are largely replaced by mucous-secreting goblet cells. The damage is greater in people who smoke both marijuana and tobacco.¹³⁰ Overproduction of mucus by the increased numbers of mucous-secreting cells in the presence of decreased numbers of ciliated cells tends to leave coughing as the only major mechanism to remove mucus from the airways; this might explain the relatively high proportion of marijuana smokers who complain of chronic cough and phlegm production.¹⁴⁸

A 1998 study has shown that both marijuana and tobacco smokers have significantly more cellular and molecular abnormalities in bronchial epithelium cells than nonsmokers; these changes are associated with increased risk of cancer.¹² The tobacco-only smokers in that study smoked an average of 25 cigarettes per day, whereas the marijuana-only smokers smoked an average of 21 marijuana cigarettes per week. Although the marijuana smokers smoked far fewer cigarettes, their cellular abnormalities were equivalent to or greater than those seen in tobacco smokers. This and earlier studies have shown that such abnormalities are greatest in people who smoke both marijuana and tobacco; hence, marijuana and tobacco smoke might have additive effects on airway tissue.^{12,43,56} Tenant¹⁵⁰ found similar results in U.S. servicemen who suffered from respiratory symptoms and were heavy hashish smokers. (Hashish is the resin from the marijuana plant.)

Chronic Obstructive Pulmonary Disease. In the absence of epidemiological data, indirect evidence, such as nonspecific airway hyperrespon-

*Ciliated cells have hair-like projections that function to transport mucus toward the mouth by rapid wave-like motion.

siveness and measures of lung function, offers an indicator of the vulnerability of marijuana smokers to COPD.¹⁵⁴ For example, the methacholine provocative challenge test, used to evaluate airway hyperresponsiveness, showed that tobacco smokers develop more airway hyperresponsiveness. But no such correlation has been shown between marijuana smoking and airway hyperresponsiveness.

There is conflicting evidence on whether regular marijuana use harms the small airways of the lungs. Bloom and co-workers found that an average of one joint smoked per day significantly impaired the function of small airways.¹⁵ But Tashkin and co-workers¹⁴⁶ did not observe such damage among heavier marijuana users (three to four joints per day for at least 10 years), although they noted a narrowing of large central airways. Tashkin and co-workers' long-term study, which adjusted for age-related decline in lung function (associated with an increased risk for developing COPD), showed an accelerated rate of decline in tobacco smokers but not in marijuana smokers.¹⁴⁷ Thus, the question of whether usual marijuana smoking habits are enough to cause COPD remains open.

Conclusion. Chronic marijuana smoking might lead to acute and chronic bronchitis and extensive microscopic abnormalities in the cells lining the bronchial passageways, some of which may be premalignant. These respiratory symptoms are similar to those of tobacco smokers, and the combination of marijuana and tobacco smoking augments these effects. At the time of this writing, it had not been established whether chronic smoking marijuana causes COPD, but there is probably an association.

HIV/AIDS Patients

The relationship between marijuana smoking and the natural course of AIDS is of particular concern because HIV patients are the largest group who report using marijuana for medical purposes. Marijuana use has been linked both to increased risk of progression to AIDS in HIV-seropositive patients and to increased mortality in AIDS patients.

For unknown reasons, marijuana use is associated with increased mortality among men with AIDS but not among the general population.¹³⁸ (The relative risk of AIDS mortality for current marijuana users in this 12-year study was 1.90, indicating that almost twice as many marijuana users died of AIDS as did noncurrent marijuana users.) Never-married men used twice as much marijuana as married men and accounted for 83% of the AIDS deaths in the study. The authors of the study note that, while marital status is insufficient to adjust for lifestyle factors—particularly, homosexual behavior—a substantial proportion of the never-married men with AIDS were probably homosexuals or bisexuals. That raises the pos-

sibility that the association of marijuana use with AIDS deaths might be related to indirect factors, such as use of other drugs or high-risk sexual behavior, both of which increase risks of infection to which AIDS patients are more susceptible. The higher mortality of AIDS patients who were current marijuana users also raises the question of whether this was because patients increased their use of marijuana at the endstages of the disease to treat their symptoms. However, the association between marijuana use and AIDS deaths was similar even when the subjects who died earliest in the first five years of this 12-year study, and who were presumably the most sick, were excluded from the analysis. In summary, it is premature to conclude what the underlying causes of this association might be.

For the general population, the mortality associated with marijuana use was lower than that associated with cigarette smoking, and tobacco smoking was not an independent risk factor in AIDS mortality. The authors of the study described above concluded that therapeutic use of marijuana did not contribute to the increased mortality among men with AIDS.

Marijuana use has been associated with a higher prevalence of HIV seropositivity in cross-sectional studies,⁸⁴ but the relationship of marijuana to the progression to AIDS in HIV-seropositive patients is a reasonable question. It remains unclear whether marijuana smoking is an independent risk factor in the progression of AIDS in HIV-seropositive men. Marijuana use did not increase the risk of AIDS in HIV-seropositive men in the Multicenter AIDS Cohort Study, in which 1,795 HIV-seropositive men were studied for 18 months,⁸⁴ or in the San Francisco Men's Health Study, in which 451 HIV-seropositive men were studied for six years.³⁴ In contrast, the Sydney AIDS Project in Australia, in which 386 HIV-seropositive men were studied for 12 months,¹⁵² reported that marijuana use was associated with increased risk of progression to AIDS. The results of the Sydney study are less reliable than those of the other two studies noted; it was the shortest of the studies and, according to the 1993 definition of AIDS, many of the subjects probably already had AIDS at the beginning of the study.*

The most compelling concerns regarding marijuana smoking in HIV/AIDS patients are the possible effects of marijuana on immunity.¹¹¹ Reports of opportunistic fungal and bacterial pneumonia in AIDS patients who used marijuana suggest that marijuana smoking either suppresses the immune system³³ or exposes patients to an added burden of patho-

*In 1993 the diagnosis of AIDS was expanded to include anyone with a CD4 count of less than 200. Prior to 1993 this alone would have been insufficient for a diagnosis of AIDS.

gens.²¹ In summary, patients with preexisting immune deficits due to AIDS should be expected to be vulnerable to serious harm caused by smoking marijuana. The relative contribution of marijuana smoke versus THC or other cannabinoids is not known.

Carcinogenicity

The gas and tar phases of marijuana and tobacco smoke contain many of the same compounds. Furthermore, the tar phase of marijuana smoke contains higher concentrations of polycyclic aromatic hydrocarbons (PAHs), such as the carcinogen benzopyrene. The higher content of carcinogenic PAHs in marijuana tar and the greater deposition of this tar in the lung might act in conjunction to amplify the exposure of a marijuana smoker to carcinogens. For those reasons the carcinogenicity of marijuana smoke is an important concern.

It is more difficult to collect the epidemiological data necessary to establish or refute the link between marijuana smoke and cancer than that between tobacco smoke and cancer. Far fewer people smoke only marijuana than only tobacco, and marijuana smokers are more likely to underreport their smoking.

Case Studies. Results of several case series suggest that marijuana might play a role in the development of human respiratory cancer. Reports indicate an unexpectedly large proportion of marijuana users among people with lung cancer^{141,149} and cancers of the upper aerodigestive tract—that is, the oral cavity, pharynx, larynx, and esophagus—that occur before the age of 45.^{36,39,149} Respiratory tract cancers associated with heavy tobacco and alcohol consumption are not usually seen before the age of 60,¹⁵⁴ and the occurrence of such cancers in marijuana users younger than 60 suggests that long-term marijuana smoking potentiates the effects of other risk factors, such as tobacco smoking, and is a more potent risk factor than tobacco and alcohol use in the early development of respiratory cancers. Most studies lack the necessary comparison groups to calculate the isolated effect of marijuana use on cancer risk. Many marijuana smokers also smoke tobacco, so when studies lack information regarding cigarette smoking status, there is no way to separate the effects of marijuana smoke and tobacco smoke.

Epidemiological Evidence. As of this writing, Sidney and co-workers¹³⁹ had conducted the only epidemiological study to evaluate the association between marijuana use and cancer. The study included a cohort of about 65,000 men and women 15–49 years old. Marijuana users were defined as those who had used marijuana on six or more occasions. Among the 1,421

cases of cancer in this cohort, marijuana use was associated only with an increased risk of prostate cancer in men who did not smoke tobacco. In these relatively young HMO clients, no association was found between marijuana use and other cancers, including all tobacco-related cancers, colorectal cancer, and melanoma. The major limitation associated with interpreting this study is that the development of lung cancer requires a long exposure to smoking, and most marijuana users quit before this level of exposure is achieved. In addition, marijuana use has been widespread in the United States only since the late 1960s; therefore, despite the large cohort size there might not have been a sufficient number of heavy or long-term marijuana smokers to reveal an effect.

Cellular and Molecular Studies. In contrast with clinical studies, cellular and molecular studies have provided strong evidence that marijuana smoke is carcinogenic. Cell culture studies implicate marijuana smoke in the development of cancer. Prolonged exposure of hamster lung cell cultures to marijuana smoke led to malignant transformations,⁹⁴ and exposure of human lung explants to marijuana smoke resulted in chromosomal and DNA alterations.¹⁵⁴ The tar from marijuana smoke also induced mutations similar to those produced by tar from the same quantity of tobacco in a common bacterial assay for mutagenicity.¹⁵⁸

Molecular studies also implicate marijuana smoke as a carcinogen. Proto-oncogenes and tumor suppressor genes are a group of genes that affect cell growth and differentiation. Normally, they code for proteins that control cellular proliferation. Once mutated or activated, they produce proteins that cause cells to multiply rapidly and out of control, and this results in tumors or cancer.* When the production of these proteins was evaluated in tissue biopsies taken from marijuana, tobacco, and marijuana plus tobacco smokers, and nonsmokers, two of them (EGFR and Ki-67) were markedly higher in the marijuana smokers than in the nonsmokers and the tobacco smokers. Moreover, the effects of marijuana and tobacco were additive.¹³¹ Thus, in relatively young smokers of marijuana, particularly those who smoke both marijuana and tobacco, marijuana is implicated as a risk factor for lung cancer.

DNA alterations are known to be early events in the development of cancer, and have been observed in the lymphocytes of pregnant marijuana smokers and in those of their newborns.⁴ This is an important study

*Some of the genes involved in the development of lung cancer include those that encode for Ki-67 (a nuclear proliferation protein responsible for cell division), the p53 tumor suppressor (a protein that normally suppresses cell growth), and epidermal growth factor receptor (EGFR) (a receptor found on a variety of cell types, especially epithelial cells, that promotes cellular growth and proliferation when bound to epidermal growth factor).

because the investigators were careful to exclude tobacco smokers—a problem in previous studies that cited mutagenic effects of marijuana smoke.^{26,53,63,142} The same investigators found similar effects in previous studies among tobacco smokers,^{5,6} so the effects cannot be attributed solely to THC or other cannabinoids. Although it can be determined only by experiment, it is likely that the smoke contents—other than cannabinoids—are responsible for a large part of the mutagenic effect.

Preliminary findings suggest that marijuana smoke activates cytochrome P4501A1 (CYP1A1), the enzyme that converts PAHs, such as benz[α]pyrene, into active carcinogens.⁹⁹ Bronchial epithelial cells in tissue biopsies taken from marijuana smokers show more binding to CYP1A1 antibodies than do comparable cells in biopsies from nonsmokers (D. Tashkin, IOM workshop). That suggests that there is more of CYP1A1 itself in the bronchial cells of marijuana smokers, but different experimental methods will be needed to establish that possibility.

Conclusions

There is no conclusive evidence that marijuana causes cancer in humans, including cancers usually related to tobacco use. However, cellular, genetic, and human studies all suggest that marijuana smoke is an important risk factor for the development of respiratory cancer. More definitive evidence that habitual marijuana smoking leads or does not lead to respiratory cancer awaits the results of well-designed case control epidemiological studies. It has been 30 years since the initiation of widespread marijuana use among young people in our society, and such studies should now be feasible.

The following studies or activities would be useful in providing data that could more precisely define the health risks of smoking marijuana.

1. Case control studies to determine whether marijuana use is associated with an increased risk of respiratory cancer. Despite the lack of compelling epidemiological evidence, findings from the biochemical, cellular, immunological, genetic, tissue, and animal studies cited above strongly suggest that marijuana is a risk factor for human cancer. What is required to address that hypothesis more convincingly is a population-based case control study of sufficiently large numbers of people with lung cancer and upper aerodigestive tumors (cancers of the oral cavity and pharynx, larynx, and esophagus), as well as noncancer controls, to demonstrate a statistically significant association, if one exists. Because of the long period required for induction of human carcinomas and the infrequent use of marijuana in the general U.S. population before 1966, no epidemiological studies so far have been extensive enough to measure the

association between marijuana and cancer adequately. However, epidemiological investigation of this association is probably possible now in that some 30 years have elapsed since the start of widespread marijuana use in the United States among teenagers and young adults.

2. Molecular markers of respiratory cancer progression in marijuana smokers. If an epidemiological association between marijuana use and risk of respiratory cancer is demonstrated, studies would be warranted to explore the presence of molecular markers—such as TP53, p16, NAT2, and GSTM1—that could be predictive of genetically increased risk of carcinogenesis in marijuana users.

3. Prospective epidemiological studies of populations with HIV seropositivity or at high risk for HIV infection.* Because HIV/AIDS patients constitute the largest group that reports smoking marijuana for medical purposes and they are particularly vulnerable to immunosuppressive effects, there is a pressing need for a better understanding of the relative risk posed by and the rewards of smoking marijuana. Such studies should include history of marijuana use in the analysis of potential risk factors for seroconversion and acquisition of opportunistic infections or progression to AIDS. The studies could be carried out in the context of any federally approved clinical trials of medical marijuana in immunocompromised patients and should provide a follow-up period long enough to capture potential adverse events.

4. Regularized recording of marijuana use by patients. Although marijuana is the most commonly used illicit drug, medical providers often do not question patients about marijuana use and rarely document its use.¹⁰² Among 452 Kaiser Permanente patients who reported daily or almost daily marijuana use, physicians recorded marijuana use in only 3% of their medical records (S. Sidney, IOM workshop).

5. Additional cellular, animal, and human studies to investigate the effects of THC and marijuana on immune function. The effects studied should include effects on proinflammatory versus immunosuppressive cytokines and on the function of leukocytes that present antigen to T cells.

The question that needs to be addressed is whether THC or marijuana is a risk factor for HIV infection, for progression to more severe stages of

*A *prospective study* is one in which a group of subjects is identified and then studied over the course of time. Such a study allows an experimenter to balance different factors that may contribute to the study outcome. For example, age, family history, and smoking are risk factors for lung cancer. In a prospective study, these factors can be balanced to measure how much smoking increases the risk of lung cancer. A *retrospective study* is one in which people with a particular disease are identified and their histories are studied. Such studies are easier and less expensive to conduct, but they generally lack the explanatory power of prospective studies.

AIDS, or for opportunistic infection among HIV-positive patients. Studies are needed to determine the effects of marijuana use on the function of alveolar macrophages. It would be important to compare the HIV infectivity and replication of alveolar macrophages harvested from habitual marijuana users with those harvested from nonusers or infrequent marijuana users. Cell culture studies could be used to compare the susceptibility of HIV-infected alveolar macrophages to additional infection with opportunistic pathogens. Similarly, further studies on cell cultures of peripheral blood mononuclear cells could be used to assess the effects of exposure to THC on HIV infectivity and replication.

Cardiovascular System

Marijuana smoke and oral THC can cause tachycardia (rapid heart beat) in humans, 20–100% above baseline.^{57,85} The increase in heart rate is greatest in the first 10–20 minutes after smoking and decreases sharply and steadily; depending on whether smoked marijuana or oral THC is used, this can last three or five hours, respectively.^{68,95} In some cases, blood pressure increases while a person is in a reclining position but decreases inordinately on standing, resulting in postural hypotension (decreased blood pressure due to changing posture from a lying or sitting position to a standing position, which can cause dizziness and faintness). In contrast with acute administration of THC, chronic oral ingestion of THC reduces heart rate in humans.¹³

In animals, THC decreases heart rate and blood pressure.^{57,156} However, most of the animal studies have been conducted in anesthetized animals, and anesthesia causes hypertension. Thus, those studies should be interpreted as reports on the effects of cannabinoids in hypertensive subjects. The results of the animal and human studies are consistent with the conclusion that cannabinoids are hypotensive at high doses in animals, as well as humans.¹⁵⁶

Tolerance can appear after a few days of frequent daily administration (two or three doses per day) of oral THC or marijuana extract, with heart rate decreasing, reclining blood pressure falling, and postural hypotension disappearing.⁷³ Thus, the intensity of the effects depends on frequency of use, dose, and even body position.

The cardiovascular changes have not posed a health problem for healthy, young users of marijuana or THC. However, such changes in heart rate and blood pressure could present a serious problem for older patients, especially those with coronary arterial or cerebrovascular disease. Cardiovascular diseases are the leading causes of death in the United States (coronary heart disease is first; stroke is third), so any effect of mari-

juana use on cardiovascular disease could have a substantial impact on public health (S. Sidney, IOM workshop). The magnitude of the impact remains to be determined as chronic marijuana users from the late 1960s enter the age when coronary arterial and cerebrovascular diseases become common. Smoking marijuana is also known to decrease maximal exercise performance. That, with the increased heart rate, could theoretically induce angina (S. Sidney, IOM workshop), so, this raises the possibility that patients with symptomatic coronary artery disease should be advised not to smoke marijuana, and THC might be contraindicated in patients with restricted cardiovascular function.

Reproductive System

Animal Studies. Marijuana and THC can inhibit many reproductive functions on a short-term basis. In both male and female animals, THC injections suppress reproductive hormones and behavior.^{107,159} Studies have consistently shown that injections of THC result in rapid, dose-dependent suppression of serum luteinizing hormone (LH).⁷⁰ (LH is the pituitary hormone that stimulates release of the gonadal hormones, testosterone and estrogen.) Embryo implantation also appears to be inhibited by THC. But it does not necessarily follow that marijuana use will interfere with human reproduction. With few exceptions, the animal studies are based on acute treatments (single injections) or short-term treatments (THC injections given over a series of days). The results are generally observed for only several hours or in females sometimes for only one ovulatory cycle.

Acute treatments with cannabinoids—including THC, CBD, cannabinol, and anandamide—can decrease the fertilizing capacity of sea urchin sperm.¹³⁵⁻¹³⁷ The sea urchin is only a distant relative of humans, but the cellular processes that regulate fertilization are similar enough that one can expect a similar effect in humans. However, the effect of cannabinoids on the capacity of sperm to fertilize eggs is reversible and is observed at concentrations of 6–100 μM ,^{136,137} which are higher than those likely to be experienced by marijuana smokers. The presence of cannabinoid receptors in sperm suggests the possibility of a natural role for anandamide in modulating sperm function during fertilization. However, it remains to be determined whether smoked marijuana or oral THC taken in prescribed doses has a clinically significant effect on the fertilizing capacity of human sperm.

Exposure to THC *in utero* can result in long-term changes. Many *in utero* effects interfere with embryo implantation (see review by Wenger and co-workers¹⁵⁹). Exposure to THC shortly before or after birth can result in impaired reproductive behavior in mice when they reach adult-

hood: females are slower to show sexual receptivity, and males are slower to mount.¹⁰⁷

Although THC can act directly on endocrine tissues, such as the testes and ovaries, it appears to affect reproductive physiology through its actions on the brain, somewhere other than the pituitary. Some of the effects of THC are exerted through its action on stress hormones, such as cortisol.⁷⁰

Human Studies. The few human studies are consistent with the acute animal studies: THC inhibits reproductive functions. However, studies of men and women who use marijuana regularly have yielded conflicting results and show either depression of reproductive hormones, no effect, or only a short-term effect. Overall, the results of human studies are consistent with the hypothesis that THC inhibits LH on a short-term basis but not in long-term marijuana users. In other words, long-term users develop tolerance to the inhibitory effect of THC on LH. The results in men and women are similar, with the added consideration of the menstrual cycle in women; the acute effects of THC appear to vary with cycle stage. THC appears to have little effect during the follicular phase (the phase after menses and before ovulation) and to inhibit the LH pulse during the luteal phase (the phase after ovulation and before menses).¹⁰³ In brief, although there are no data on fertility itself, marijuana or THC would probably decrease human fertility—at least in the short term—for both men and women. And it is reasonable to predict that THC can interfere with early pregnancy, particularly with implantation of the embryo. Like tobacco smoke, marijuana smoke is highly likely to be harmful to fetal development and should be avoided by pregnant women and those who might become pregnant in the near future. Nevertheless, although fertility and fetal development are important concerns for many, they are unlikely to be of much concern to people with seriously debilitating or life-threatening diseases. The well-documented inhibition of reproductive functions by THC is thus not a serious concern for evaluating the short-term medical use of marijuana or specific cannabinoids.

The results of studies of the relationship between prenatal marijuana exposure and birth outcome have been inconsistent (reviewed in 1995 by Cornelius and co-workers³⁰). Except for adolescent mothers, there is little evidence that gestation is shorter in mothers who smoke marijuana.³⁰ Several studies of women who smoked marijuana regularly during pregnancy show that they tend to give birth to lower weight babies.^{46,65} Mothers who smoke tobacco also give birth to lower weight babies, and the relative contributions of smoking and THC are not known from these studies.

Babies born to mothers who smoked marijuana during pregnancy

weighed an average of 3.4 ounces less than babies born to a control group of mothers who did not smoke marijuana; there was no statistically significant difference in either gestational age or frequency of congenital abnormalities.¹⁶⁴ Those results were based on women whose urine tests indicated recent marijuana exposure. However, when the analysis was based only on self-reports of marijuana use (without verification by urine tests), there was no difference in weight between babies born to women who reported themselves as marijuana smokers and those born to women who reported that they did not smoke marijuana. That raises an important concern about the methods used to measure the effects of marijuana smoking in any study, perhaps even more so in studies on the effects of marijuana during pregnancy, when subjects might be less likely to admit to smoking marijuana. (The study was conducted in the last trimester of pregnancy, and there was no information about the extent of marijuana use earlier in pregnancy.)

For most of these studies, much of the harm associated with marijuana use is consistent with that associated with tobacco use, and smoking is an important factor, so the contribution of cannabinoids cannot be confirmed. However, Jamaican women who use marijuana rarely smoke it; but instead prepare it as tea.³⁷ In a study of neonates born to Jamaican women who did or did not ingest marijuana during pregnancy, there was no difference in neurobehavioral assessments made at three days after birth and at one month.³⁸ A limitation of the study is that there was no direct measure of marijuana use. Estimates of marijuana use were based on self-reports, which might be more accurate in Jamaica than in the United States because less social stigma is associated with marijuana use in Jamaica but still are less reliable than direct measures.

Newborns of mothers who smoke either marijuana or tobacco have statistically significantly higher mutation rates than those of non-smokers.^{4,5}

Since 1978, the Ottawa Prenatal Prospective Study has measured the cognitive functions of children born to mothers who smoked marijuana during pregnancy.⁴⁷ Children of mothers who smoked either moderately (one to six marijuana cigarettes per week) or heavily (more than six marijuana cigarettes per week) have been studied from the age of four days to 9–12 years. It is important to keep in mind that studies like this provide important data about the risks associated with marijuana use during pregnancy, but they do not establish the *causes* of any such association.

The children in the different marijuana exposure groups showed no lasting differences in global measures of intelligence, such as language development, reading scores, and visual or perceptual tests. Moderate cognitive deficits were detectable among these children when they were

four days old and again at four years, but the deficits were no longer apparent at five years.

Prenatal marijuana exposure was not, however, without lasting effect. At ages 5–6 years and 9–12 years, children in the same study who were prenatally exposed to tobacco smoke scored lower on tests of language skills and cognitive functioning.⁴⁸ In another study,^{49,50} 9 to 12 year olds who were exposed to marijuana prenatally scored lower than control subjects on tasks associated with “executive function,” a term used by psychologists to describe a person’s ability to plan, anticipate, and suppress behaviors that are incompatible with a current goal.⁵⁰ It was reflected in how the mothers described their children. Mothers of the marijuana-exposed children were more likely to describe their offspring as hyperactive or impulsive than were mothers of control children. The alteration in executive function was not seen in children born to tobacco smokers. The underlying causes might be the marijuana exposure or might be more closely related to the reasons underlying the mothers’ use of marijuana during pregnancy.

Mice born to dams injected with the endogenous cannabinoid, anandamide, during the last trimester of pregnancy also showed delayed effects. No effect of anandamide treatment during pregnancy was detected until the mice were adults (40 days old), at which time they showed behavioral changes that are common to the effects of other psychotropic drugs or prenatal stress.⁴⁵ As with the children born to mothers who smoked marijuana, it is not known what aspect of the treatment caused the effect. The dams might have found the dose (20 mg/kg of body weight) of anandamide aversive, in which case the effect could have resulted from generalized stress, as opposed to a cannabinoid-specific effect. Either is possible. Despite the uncertainty as to the underlying causes of the effects of prenatal exposure to cannabinoid drugs, it is prudent to advise against smoking marijuana during pregnancy.

SUMMARY AND CONCLUSIONS

This chapter summarizes the harmful effects of marijuana on individual users and, to a lesser extent, on society. The harmful effects on individuals were considered from the perspective of possible medical use of marijuana and can be divided into acute and chronic effects. The vast majority of evidence on harmful effects of marijuana is based on *smoked* marijuana, and, except for the psychoactive effects that can be reasonably attributed to THC, it is not possible to distinguish the drug effects from the effects of inhaling smoke from burning plant material.

For most people the primary adverse effect of *acute* marijuana use is diminished psychomotor performance; it is inadvisable for anyone under

the influence of marijuana to operate any equipment that might put the user or others in danger (such as driving or operating complex equipment). Most people can be expected to show impaired performance of complex tasks, and a minority experience dysphoria. People with or at risk of psychiatric disorders (including substance dependence) are particularly vulnerable to developing marijuana dependence, and marijuana use would be generally contraindicated for them. The short-term immunosuppressive effects are not well established; if they exist at all, they are probably not great enough to preclude a legitimate medical use. The acute side effects of marijuana use are within the risks tolerated for many medications.

The *chronic* effects of marijuana are of greater concern for medical use and fall into two categories: the effects of chronic smoking and the effects of THC. Marijuana smoke is like tobacco smoke in that it is associated with increased risk of cancer, lung damage, and poor pregnancy outcome. Smoked marijuana is unlikely to be a safe medication for any chronic medical condition. The second category is that associated with dependence on the psychoactive effects of THC. Despite past skepticism, it has been established that, although it is not common, a vulnerable subpopulation of marijuana users can develop dependence. Adolescents, particularly those with conduct disorders, and people with psychiatric disorders, or problems with substance abuse appear to be at greater risk for marijuana dependence than the general population.

As a cannabinoid drug delivery system, marijuana cigarettes are not ideal in that they deliver a variable mixture of cannabinoids and a variety of other biologically active substances, not all of which are desirable or even known. Unknown substances include possible contaminants, such as fungi or bacteria.

Finally, there is the broad social concern that sanctioning the medical use of marijuana might lead to an increase in its use among the general population. No convincing data support that concern. The existing data are consistent with the idea that this would not be a problem if the medical use of marijuana were as closely regulated as the use of other medications that have abuse potential, but we acknowledge a lack of data that directly address the question. Even if there were evidence that the medical use of marijuana would decrease the perception that it can be a harmful substance, this is beyond the scope of laws regulating the approval of therapeutic drugs. Those laws concern scientific data related to the safety and efficacy of drugs for individual use; they do not address perceptions or beliefs of the general population.

Marijuana is not a completely benign substance. It is a powerful drug with a variety of effects. However, except for the harm associated with smoking, the adverse effects of marijuana use are within the range toler-

ated for other medications. Thus, the safety issues associated with marijuana do not preclude some medical uses. But the question remains: Is it effective? That question is covered here in two chapters: chapter 2 summarizes what has been learned about the biological activity of cannabinoids in the past 15 years through research in the basic sciences, and chapter 4 reviews clinical data on the effectiveness of marijuana and cannabinoids for the treatment of various medical conditions.

Three factors influence the safety of marijuana or cannabinoid drugs for medical use: the delivery system, the use of plant material, and the side effects of cannabinoid drugs. (1) Smoking marijuana is clearly harmful, especially in people with chronic conditions, and is not an ideal drug delivery system. (2) Plants are of uncertain composition, which renders their effects equally uncertain, so they constitute an undesirable medication. (3) The side effects of cannabinoid drugs are within the acceptable risks associated with approved medications. Indeed, some of the side effects, such as anxiety reduction and sedation, might be desirable for some patients. As with many medications, there are people for whom they would probably be contraindicated.

CONCLUSION: Present data on drug use progression neither support nor refute the suggestion that medical availability would increase drug abuse. However, this question is beyond the issues normally considered for medical uses of drugs, and it should not be a factor in the evaluation of the therapeutic potential of marijuana or cannabinoids.

CONCLUSION: A distinctive marijuana withdrawal syndrome has been identified, but it is mild and short lived. The syndrome includes restlessness, irritability, mild agitation, insomnia, sleep EEG disturbance, nausea, and cramping.

CONCLUSION: Numerous studies suggest that marijuana smoke is an important risk factor in the development of respiratory disease.

RECOMMENDATION: Studies to define the individual health risks of smoking marijuana should be conducted, particularly among populations in which marijuana use is prevalent.

REFERENCES

1. Adams IB, Martin BR. 1996. Cannabis: Pharmacology and toxicology in animals and humans. *Addiction* 91:1585–1614.
2. American Psychiatric Association. 1987. *Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R)*. 3rd ed., revised. Washington, DC: American Psychiatric Association.
3. American Psychiatric Association. 1994. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. 4th ed. Washington, DC: American Psychiatric Association.
4. Ammenheuser MM, Berenson AB, Babiak AE, Singleton CR, Whorton Jr EB. 1998. Frequencies of *hprt* mutant lymphocytes in marijuana-smoking mothers and their newborns. *Mutation Research* 403:55–64.
5. Ammenheuser MM, Berenson NJ, Stiglich EB, Whorton Jr EB, Ward Jr JB. 1994. Elevated frequencies of *hprt* mutant lymphocytes in cigarette-smoking mothers and their newborns. *Mutation Research* 304:285–294.
6. Ammenheuser MM, Hastings DA, Whorton Jr EB, Ward Jr JB. 1997. Frequencies of *hprt* mutant lymphocytes in smokers, non-smokers, and former smokers. *Environmental and Molecular Mutagenesis* 30:131–138.
7. Anthenelli RM, Schuckit MA. 1992. Genetics. In: Lowinson JH, Ruiz P, Millman RB, Editors, *Substance Abuse: A Comprehensive Textbook*. 2nd ed. Baltimore, MD: Williams & Wilkins. Pp. 39–50.
8. Anthony JC, Warner LA, Kessler RC. 1994. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology* 2:244–268.
9. Bailey SL, Flewelling RL, Rachal JV. 1992. Predicting continued use of marijuana among adolescents: The relative influence of drug-specific and social context factors. *Journal of Health and Social Behavior* 33:51–66.
10. Baldwin GC, Tashkin DP, Buckley DM, Park AN, Dubinett SM, Roth MD. 1997. Marijuana and cocaine impair alveolar macrophage function and cytokine production. *American Journal of Respiratory and Critical Care Medicine* 156:1606–1613.
11. Barbers RG, Gong HJ, Tashkin DP, Oishi J, Wallace J M. 1987. Differential examination of bronchoalveolar lavage cells in tobacco cigarette and marijuana smokers. *American Review of Respiratory Disease* 135:1271–1275.
12. Barsky SH, Roth MD, Kleerup EC, Simmons M, Tashkin DP. 1998. Histopathologic and molecular alterations in bronchial epithelium in habitual smokers of marijuana, cocaine, and/or tobacco. *Journal of the National Cancer Institute* 90:1198–1205.
13. Benowitz NL, Jones RT. 1975. Cardiovascular effects of prolonged delta-9-tetrahydrocannabinol ingestion. *Clinical Pharmacology and Therapeutics* 18:287–297.
14. Block RI, Ghoneim MM. 1993. Effects of chronic marijuana use on human cognition. *Psychopharmacology* 110:219–228.
15. Bloom JW, Kaltborn WT, Paoletti P, Camilli A, Lebowitz MS. 1987. Respiratory effects of non-tobacco cigarettes. *British Medical Journal* 295:516–518.
16. Bornheim LM, Kim KY, Li J, Perotti BY, Benet LZ. 1995. Effect of cannabidiol pretreatment on the kinetics of tetrahydrocannabinol metabolites in mouse brain. *Drug Metabolism and Disposition (United States)* 23:825–831.
17. British Medical Association. 1997. *Therapeutic Uses of Cannabis*. Amsterdam, The Netherlands: Harwood Academic Publishers.
18. Brook JS, Cohen P, Brook DW. 1998. Longitudinal study of co-occurring psychiatric disorders and substance use. *Journal of the American Academy of Child and Adolescent Psychiatry* 37:322–330.

19. Budney AJ, Radonovich KJ, Higgins ST, Wong CJ. 1998. Adults seeking treatment for marijuana dependence: A comparison with cocaine-dependent treatment seekers. *Experimental and Clinical Psychopharmacology* 6:419–426.
20. Burns LA, Meade BJ, Munson AE. 1996. Toxic responses of the immune system. In: CD Klaassen, MO Amdur, and J Dou, Editors, *Casarett and Dou, Toxicology: The Basic Science of Poisons*. 5th ed. New York: McGraw-Hill. Pp. 355–402.
21. Caiaffa WT, Vlahov D, Graham N, Astemborski J, Solomon L, Nelson KE, Muñoz. 1994. Drug smoking, *Pneumocystis carinii* pneumonia, and immunosuppression increase risk of bacterial pneumonia in human immunodeficiency virus-seropositive injection drug users. *American Journal of Respiratory and Critical Care Medicine* 150:1493–1498.
22. Campbell AM, Evans M, Thompson JL, Williams MR. 1971. Cerebral atrophy in young cannabis smokers. *Lancet* 2:1219–1224.
23. Chait LD, Pierri J. 1992. Effects of smoked marijuana on human performance: A critical review. In: L Murphy and A Bartke, Editors, *Marijuana/Cannabinoids: Neurobiology and Neurophysiology*. Boca Raton, FL: CRC Press. Pp. 387–424.
24. Charalambous A, Marciniak G, Shiue CY, Dewey SL, Schlyer DJ, Wolf AP, Makriyannis A. 1991. PET studies in the primate brain and biodistribution in mice using (–)-5'-18F-delta 8-THC. *Pharmacology Biochemistry and Behavior* 40:503–507.
25. Chen K, Kandel DB, Davies M. 1997. Relationships between frequency and quantity of marijuana use and last year proxy dependence among adolescents and adults in the United States. *Drug and Alcohol Dependence* 46:53–67.
26. Chiesara E, Rizzi R. 1983. Chromosome damage in heroin-marijuana and marijuana addicts. *Archives of Toxicology Supplement* 6:128–130.
27. Cleeland CS, Gonin R, Hatfield AK, Edmonson JH, Blum RH, Stewart JA, Pandya KJ. 1994. Pain and its treatment in outpatients with metastatic cancer. *New England Journal of Medicine* 330:592–596.
28. Co BT, Goodwin DW, Gado M, Mikhael M, Hill SY. 1977. Absence of cerebral atrophy in chronic cannabis users by computerized transaxial tomography. *Journal of the American Medical Association* 237:1229–1230.
29. Cohen MJ, Rickles Jr WH. 1974. Performance on a verbal learning task by subjects of heavy past marijuana usage. *Psychopharmacologia* 37:323–330.
30. Cornelius MD, Taylor PM, Geva D, Day NL. 1995. Prenatal tobacco and marijuana use among adolescents: Effects on offspring gestational age, growth, and morphology. *Pediatrics* 95(5):738–743.
31. Crowley TJ, Macdonald MJ, Whitmore EA, Mikulich SK. 1998. Cannabis dependence, withdrawal, and reinforcing effects among adolescents with conduct symptoms and substance use disorders. *Drug and Alcohol Dependence* 50:27–37.
32. Crowley TJ, Rhine MW. 1985. The substance use disorders. In: Simons RC, Editor, *Understanding Human Behavior in Health and Illness*. 3rd ed. Baltimore, MD: Williams & Wilkins. Pp. 730–746.
33. Denning DW, Follansbee SE, Scolaro M, et al. 1991. Pulmonary aspergillosis in the acquired immunodeficiency syndrome. *New England Journal of Medicine* 324:654–662.
34. Di Franco MJ, Sheppard HW, Hunter DJ, Tosteson TD, Ascher MS. 1996. The lack of association of marijuana and other recreational drugs with progression to AIDS in the San Francisco Men's Health Study. *Annals of Epidemiology* 6:283–289.
35. Dixon L, Haas G, Weiden PJ, Sweeney J, Frances AJ. 1991. Drug abuse in schizophrenic patients: Clinical correlates and reasons for use. *American Journal of Psychiatry* 148:224–230.
36. Donald PJ. 1991. Advanced malignancy in the young marijuana smoker. *Advances in Experimental Medicine and Biology* 288:33–56.

37. Dreher M. 1987. The evolution of a roots daughter. *Journal of Psychoactive Drugs* 19:165–170.
38. Dreher MC, Nugent K, Hudgins R. 1994. Prenatal marijuana exposure and neonatal outcomes in Jamaica: An ethnographic study. *Pediatrics* 93:254–260.
39. Endicott JN, Skipper P, Hernandez L. 1993. Marijuana and head and neck cancer. In: Friedman et al., Editors, *Drugs of Abuse, Immunity and AIDS*. New York: Plenum Press. Pp. 107–113.
40. Fehr K, Kalant H. 1981. Cannabis and health hazards. *Proceedings of an ARF/WHO Scientific Meeting on Adverse Health and Behavioral Consequences of Cannabis Use*. Fehr K, Kalant H, Editors, Toronto, Canada: Addiction Research Foundation.
41. Fleischman RW, Baker JR, Rosenkrantz H. 1979. Pulmonary pathologic changes in rats exposed to marijuana smoke for one year. *Toxicology and Applied Pharmacology* 47:557–566.
42. Fligiel SE, Beals TF, Tashkin DP, Paule MG, Scallet AC, Ali SF, Bailey JR, Slikker WJ. 1991. Marijuana exposure and pulmonary alterations in primates. *Pharmacology, Biochemistry and Behavior* 40:637–642.
43. Fligiel SEG, Roth MD, Kleerup EC, Barsky SH, Simmons M, Tashkin DP. 1997. Tracheobronchial histopathology in habitual smokers of cocaine, marijuana, and/or tobacco. *Chest* 112:319–326.
44. Foley K. 1997. Competent care for the dying instead of physician-assisted suicide. *New England Journal of Medicine* 336:54–58.
45. Fride E, Mechoulam R. 1996. Ontogenetic development of the response to anandamide and delta 9-tetrahydrocannabinol in mice. *Brain Research, Developmental Brain Research* 95:131–134.
46. Fried PA. 1982. Marijuana use by pregnant women and effects on offspring: An update. *Neurobehavioral Toxicology and Teratology* 4:451–454.
47. Fried PA. 1995. The Ottawa Prenatal Prospective Study (OPPS): Methodological issues and findings—it's easy to throw the baby out with the bath water. *Life Sciences* 56:2159–2168.
48. Fried PA, O'Connell CM, Watkinson B. 1992. 60- and 72-Month follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol: Cognitive and language assessment. *Developmental and Behavioral Pediatrics* 13:383–391.
49. Fried PA, Watkinson BSL. 1997. Reading and language in 9- to 12-year-olds prenatally exposed to cigarettes and marijuana. *Neurotoxicology and Teratology* 19:171–183.
50. Fried PA, Watkinson B, Gray R. 1998. Differential effects on cognitive functioning in 9- to 12-year-olds prenatally exposed to cigarettes and marijuana. *Neurotoxicology and Teratology* 20:293–306.
51. Gardner EL. 1992. Brain reward mechanisms. In: Lowinson JH, Ruiz P, Millman RB, Editors, *Substance Abuse: A Comprehensive Textbook*. 2nd ed. Baltimore, MD: Williams and Wilkins. Pp. 70–99.
52. Georgotas A, Zeidenberg P. 1979. Observations on the effects of four weeks of heavy marijuana smoking on group interaction and individual behavior. *Comprehensive Psychiatry* 20:427–432.
53. Gilmore DG, Blood AD, Lele KP, Robbins ES, Maximillian C. 1971. Chromosomal aberrations in users of psychoactive drugs. *Archives of General Psychiatry* 24:268–272.
54. Goldstein A. 1994. Tolerance and Dependence. In: Goldstein A, Editor, *Addiction: From Biology to Drug Policy*. New York: W.H. Freeman. Pp. 73–84.
55. Golub A, Johnson BD. 1994. The shifting importance of alcohol and marijuana as gateway substances among serious drug abusers. *Journal of Studies on Alcohol* 55:607–614.

56. Gong HJ, Fligiel S, Tashkin DP, Barbers RG. 1987. Tracheobronchial changes in habitual, heavy smokers of marijuana with and without tobacco. *American Review of Respiratory Disease* 136:142–149.
57. Graham JDP. 1986. The cardiovascular action of cannabinoids. In: Mechoulam R, Editor, *Cannabinoids as Therapeutic Agents*. Boca Raton, FL: CRC Press. Pp. 159–166.
58. Grant S, London ED, Newlin DB, Villemagne VL, Liu X, Contoreggi C, Phillips RL, Kimes AS, Margolin A. 1996. Activation of memory circuits during cue-elicited cocaine craving. *Proceedings of the National Academy of Sciences, USA* 93:12040–12045.
59. Hall W, Solowij N. 1998. Adverse effects of cannabis. *The Lancet* 352:1611–1616.
60. Hall W, Solowij N, Lemon J. 1994. *The Health and Psychological Consequences of Cannabis Use*. Department of Human Services and Health, Monograph Series, No. 25. Canberra, Australia: Australian Government Publishing Service.
61. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. 1999. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology* 141:385–394.
62. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. 1999. Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology* 141:395–404.
- 62a. Heishman SJ, Huestis MA, Henningfield JE, Cone EJ. 1990. Acute and residual effects of marijuana: Profiles of plasma THC levels, physiological, subjective, and performance measures. *Pharmacology, Biochemistry, and Behavior* 37:561–565.
63. Hertha J, Obe G. 1974. Chromosomal damage in chronic users of cannabis: In vivo investigation with two-day lymphocyte cultures. *Pharmakopsychiatrie* 7:328–337.
64. Herring AC, Koh WS, Kaminski NE. 1998. Inhibition of the cyclic AMP signaling cascade and nuclear factor binding to CRE and kappa B elements by cannabitol, a minimally CNS-active cannabinoid. *Biochemical Pharmacology* 55:1013–1023.
65. Hingson R, Alpert JJ, Day N, Dooling E, Kayn H, Morelock S, Oppenheimer E, Zuckerman B. 1982. Effects of maternal drinking and marijuana use on fetal growth and development. *Pediatrics* 70:539–546.
66. Hollister LE. 1986. Health aspects of cannabis. *Pharmacological Reviews* 38:1–20.
67. Huber GL, Mahajan VK. 1988. The comparative response of the lung to marijuana or tobacco smoke inhalation. In: Chesher G, Consroe P, Musty R, Editors, *Marijuana: An International Research Report: Proceedings of Melbourne Symposium on Cannabis 2-4 September, 1987*. National Campaign Against Drug Abuse Monograph Series No. 7 Edition. Canberra: Australian Government Publishing Service. Pp. 19–24.
68. Huestis MA, Sampson AH, Holicky BJ, Henningfield JE, Cone EJ. 1992. Characterization of the absorption phase of marijuana smoking. *Clinical Pharmacology and Therapeutics* 52:31–41.
69. IOM (Institute of Medicine). 1982. *Marijuana and Health*. Washington, DC: National Academy Press.
70. Jackson AL, Murphy LL. 1997. Role of the hypothalamic-pituitary-adrenal axis in the suppression of luteinizing hormone release by delta-9-tetrahydrocannabinol. *Neuroendocrinology* 65:446–452.
71. Johnson V. 1995. The relationship between parent and offspring comorbid disorders. *Journal of Substance Abuse* 7:267–280.
72. Johnston LD, O'Malley PM, Bachman JG. 1989. Marijuana decriminalization: The impact on youth, 1975–1980. *Journal of Public Health Policy* 10:456.
73. Jones RT, Benowitz NL, Herning RI. 1981. Clinical relevance of cannabis tolerance and dependence. *Journal of Clinical Pharmacology* 21:143S–152S.
74. Jones RT, Benowitz N, Bachman J. 1976. Clinical studies of tolerance and dependence. *Annals of the New York Academy of Sciences* 282:221–239.
75. Kaklamani E, Trichopoulos D, Koutselinis A, Drouga M, Karalis D. 1978. Hashish smoking and T-lymphocytes. *Archives of Toxicology* 40:97–101.

76. Kandel DB. 1992. Epidemiological trends and implications for understanding the nature of addiction. In: O'Brien CP, Jaffe JH, Editors, *Addictive Studies*. New York: Raven Press, Ltd. Pp. 23–40.
77. Kandel DB, Chen KWLA, Kessler R, Grant B. 1997. Prevalence and demographic correlates of symptoms of last year dependence on alcohol, nicotine, marijuana and cocaine in the U.S. population. *Drug and Alcohol Dependence* 44:11–29.
78. Kandel DB, Davies M. 1992. Progression to regular marijuana involvement: phenomenology and risk factors for near-daily use. In: Glantz M, Pickens R, Editors, *Vulnerability to Drug Abuse*. Washington, DC: American Psychological Association. Pp. 211–253.
79. Kandel DB, Johnson JG, Bird HR, Canino G, Goodman SH, Lahey BB, Regier DA, Schwab-Stone M. 1997. Psychiatric disorders associated with substance use among children and adolescents: Findings from the Methods for the Epidemiology of Child and Adolescent Mental Disorders (MECA) Study. *Journal of Abnormal Child Psychology* 25:121–132.
80. Kandel DB, Raveis VH. 1989. Cessation of illicit drug use in young adulthood. *Archives of General Psychiatry* 46:109–116.
81. Kandel DB, Yamaguchi K. 1993. From beer to crack: developmental patterns of drug involvement. *American Journal of Public Health* 83:851–855.
82. Kandel DB, Yamaguchi K, Chen K. 1992. Stages of progression in drug involvement from adolescence to adulthood: Further evidence for the gateway theory. *Journal of Studies in Alcohol* 53:447–457.
83. Kaplan HB, Martin SS, Johnson RJ, Robbins CA. 1996. Escalation of marijuana use: Application of a general theory of deviant behavior. *Journal of Health and Social Behavior* 27:44–61.
84. Kaslow RA, Blackwelder WC, Ostrow DG, et al. 1989. No evidence for a role of alcohol or other psychoactive drugs in accelerating immunodeficiency in HIV-1 positive individuals: A report for the multicenter AIDS cohort study. *Journal of the American Medical Association* 261:3424–3429.
85. Kelly TH, Foltin RW, Fischman MW. 1993. Effects of smoked marijuana on heart rate, drug ratings and task performance by humans. *Behavioural Pharmacology* 4:167–178.
86. Kendler KS, Prescott CA. 1998. Cannabis use, abuse, and dependence in a population-based sample of female twins. *American Journal of Psychiatry* 155:1016.
87. Klein TW, Friedman H, Specter SC. 1998. Marijuana, immunity and infection. *Journal of Neuroimmunology* 83:102–115.
88. Koob GF, Le Moal M. 1997. Drug abuse: Hedonic homeostatic dysregulation. *Science* 278:52–58.
89. Kuehnle J, Mendelson JH, Davis KR, New PF. 1977. Computed tomographic examination of heavy marijuana smokers. *Journal of the American Medical Association* 237:1231–1232.
90. Labouvie E, Bates ME, Pandina RJ. 1997. Age of first use: Its reliability and predictive utility. *Journal of Studies on Alcohol* 58:638–643.
91. Lau RJ, Tubergen DG, Barr MJ, Domino EF, Benowitz N, Jones RT. 1976. Phytohemagglutinin-induced lymphocyte transformation in humans receiving delta-9-tetrahydrocannabinol. *Science* 192:805–807.
92. Lepore M, Liu X, Savage V, Matalon D, Gardner EL. 1996. Genetic differences in delta 9-tetrahydrocannabinol-induced facilitation of brain stimulation reward as measured by a rate-frequency curve-shift electrical brain stimulation paradigm in three different rat strains. *Life Sciences* 58:365–372.

93. Lepore M, Vorel SR, Lowinson J, Gardner EL. 1995. Conditioned place preference induced by delta 9-tetrahydrocannabinol: Comparison with cocaine, morphine, and food reward. *Life Sciences* 56:2073–2080.
94. Leuchtenberger C, Leuchtenberger R. 1976. Cytological and cytochemical studies of the effects of fresh marijuana cigarette smoke on growth and DNA metabolism of animal and human lung cultures. In: Braude MC, Szara S, Editors, *The Pharmacology of Marijuana*. New York: Raven Press.
95. Lindgren JE, Ohlsson A, Agurell S, Hollister LE, Gillespie H. 1981. Clinical effects and plasma levels of delta 9-tetrahydrocannabinol (delta 9-THC) in heavy and light users of cannabis. *Psychopharmacology (Berlin)* 74:208–212.
96. Linzen DH, Dingemans PM, Lenior ME. 1994. Cannabis abuse and the course of recent-onset schizophrenic disorders. *Archives of General Psychiatry* 51:273–279.
97. Lyons MJ., Toomey R, Meyer JM, Green AI, Eisen SA, Goldberg J, True WR, Tsuang MT. 1997. How do genes influence marijuana use? The role of subjective effects. *Addiction* 92:409–417.
98. MacCoun R, Reuter P. 1997. Interpreting Dutch cannabis policy: Reasoning by analogy in the legalization debate. *Science* 278:47–52.
99. Marques-Magallanes JA, Tashkin DP, Serafian T, Stegeman J, Roth MD. 1997. *In vivo* and *in vitro* activation of cytochrome P4501A1 by marijuana smoke. *Symposium on the Cannabinoids of the International Cannabinoid Research Society Program and Abstracts*. Stone Mountain, GA, June 1997.
100. Martellotta MC, Cossu G, Fattore L, Gessa GL, Fratta W. 1998. Self-administration of the cannabinoid receptor agonist WIN 55,212-2 in drug-naive mice. *Neuroscience* 85:327–330.
101. Mathew RJ, Wilson WH, Humphreys DF, Lowe JV, Wiethe KE. 1992. Regional cerebral blood flow after marijuana smoking. *Journal of Cerebral Blood Flow and Metabolism* 12:750–758.
102. Mathre ML. 1998. A survey on disclosure of marijuana use to health care professionals. *Journal of Psychoactive Drugs* 20:117–120.
103. Mendelson JH, Cristofaro P, Ellingboe J, Benedikt R, Mello NK. 1985. Acute effects of marijuana on luteinizing hormone in menopausal women. *Pharmacology, Biochemistry, and Behavior* 23:765–768.
104. Meyer RE, Pillard RC, Shapiro LM, Mirin SM. 1971. Administration of marijuana to heavy and casual marijuana users. *American Journal of Psychiatry* 128:198–204.
105. Model KE. 1993. The effect of marijuana decriminalization on hospital emergency room drug episodes: 1975–1978. *Journal of the American Statistical Association* 88:737–747.
106. Moulin DE, Iezzi A, Amireh R, Sharpe WKJ, Boyd D, Merskey H. 1996. Randomised trial of oral morphine for chronic non-cancer pain. *Lancet* 347:143–147.
107. Murphy LL, Gher J, Szary A. 1995. Effects of prenatal exposure to delta-9-tetrahydrocannabinol on reproductive, endocrine and immune parameters of male and female rat offspring. *Endocrine* 3:875–879.
108. Nahas GG, Osserman EF. 1991. Altered serum immunoglobulin concentration in chronic marijuana smokers. *Advances in Experimental Medicine and Biology* 288:25–32.
109. Nesse RM, Berridge KC. 1997. Psychoactive drug use in evolutionary perspective. *Science* 278:63–66.
110. Nestler EJ, Aghajanian GK. 1997. Molecular and cellular basis of addiction. *Science* 278:58–63.
111. Newell GR, Mansell PW, Wilson MB, Lynch HK, Spitz MR, Hersh EM. 1985. Risk factor analysis among men referred for possible acquired immune deficiency syndrome. *Preventive Medicine* 14:81–91.

112. NIH (National Institutes of Health). 1997. Workshop on the Medical Utility of Marijuana. Report to the Director, National Institutes of Health by the Ad Hoc Group of Experts. Bethesda, MD, February 19–20, 1997. Bethesda, MD: National Institutes of Health.
113. O'Brien CP. 1996. Drug addiction and drug abuse. In: Harmon JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, Editor, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 9th ed. New York: McGraw-Hill. Pp. 557–577.
114. O'Brien CP. 1996. Recent developments in the pharmacotherapy of substance abuse. *Journal of Consulting and Clinical Psychology* 64:677–686.
115. O'Brien CP. 1997. A range of research-based pharmacotherapies for addiction. *Science* 278:66–70.
116. O'Leary DS, Andreasen NC, Hurtig RR, Torres IJ, Flashman LA, Kesler ML, Arndt SV, Cizadlo TJ, Ponto LLB, Watkins GL, Hichwa RD. 1997. Auditory and visual attention assessed with PET. *Human Brain Mapping* 5:422–436.
117. O'Leary D, Block RI, Flaum M, Boles Ponto LL, Watkins GL, Hichwa RD. 1998. Acute marijuana effects on rCBF and cognition: A PET study. *Abstracts—Society for Neuroscience: 28th Annual Meeting*. Los Angeles, November 7–12, 1998. Washington, DC: Society for Neuroscience.
118. Ohlsson A, Lindgren J-E, Wahlen A, Agurell S, Hollister LE, Gillespie HK. 1980. Plasma delta-9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clinical Pharmacology and Therapeutics* 28:409–416.
119. Peterson RC. 1979. Importance of inhalation patterns in determining effects of marijuana use. *Lancet* 1:727–728.
120. Polen MR, Sidney S, Tekawa IS, Sadler M, Friedman D. 1993. Health care use by frequent marijuana smokers who do not smoke tobacco. *The Western Journal of Medicine* 158:596–601.
121. Pope HG, Gruber AJ, Yurgelun-Todd D. 1995. The residual neuropsychological effects of cannabis: The current status of research. *Drug and Alcohol Dependence* 38:25–34.
122. Pope HG, Yurgelun-Todd D. 1996. The residual cognitive effects of heavy marijuana use in college students. *Journal of the American Medical Association* 275:521–527.
123. Rachelefsky G, Opelz G, Mickey M, Lessin P, Kiuchi M, Silverstein M, Stiehm E. 1976. Intact humoral and cell-mediated immunity in chronic marijuana smoking. *Journal of Allergy and Clinical Immunology* 58:483–490.
124. Rickles Jr WH, Cohen MJ, Whitaker CA, McIntyre KE. 1973. Marijuana-induced state-dependent verbal learning. *Psychopharmacologia* 30:349–354.
125. Robins LN. 1980. The natural history of drug abuse. *Acta Psychiatrica Scandinavica Supplement* 284:7–20.
126. Robins LN. 1998. The intimate connection between antisocial personality and substance abuse. *Social Psychiatry and Psychiatric Epidemiology* 33:393–399.
127. Robins LN, McEvoy LT. 1990. Conduct problems as predictors of substance abuse. In: Robins L, Rutter M, Editors, *Straight and Devious Pathways from Childhood to Adulthood*. New York: Cambridge University Press. Pp. 182–204.
128. Rosenkrantz H, Fleischman RW. 1979. Effects of cannabis on lung. In: Nahas GG, Payton WDH, Editors, *Marijuana: Biological Effects*. Oxford, England: Pergamon Press. Pp. 279–299.
129. Rosenzweig MR, Leiman AL, Breedlove SM. 1996. *Biological Psychology*. Sunderland, MA: Sinauer Associates.

130. Roth MD, Arora A, Barsky SH, Kleeup EC, Simmons MS, Tashkin DP. 1998. Airway inflammation in young marijuana and tobacco smokers. *American Journal of Respiratory and Critical Care Medicine* 157:1–9.
131. Roth MD, Kleeup EC, Arora A, Barsky SH, Tashkin DP. 1996. Endobronchial injury in young tobacco and marijuana smokers as evaluated by visual, pathologic and molecular criteria. *American Review of Respiratory and Critical Care Medicine* 153 (part 2):100A.
132. SAMHSA (Substance Abuse and Mental Health Services Administration). 1998. *National Household Survey on Drug Abuse: Population Estimates 1997*. DHHS Pub. No. (SMA) 98-3250. Rockville, MD: SAMHSA, Office of Applied Studies.
133. Scheier LM, Bovtin GJ. 1996. Cognitive effects of marijuana. *Journal of the American Medical Association* 275:JAMA Letters.
134. Schneier FR, Siris SG. 1987. A review of psychoactive substance use and abuse in schizophrenia: Patterns of drug choice. *Journal of Nervous and Mental Disease* 175:641–652.
135. Schuel H, Berkery D, Schuel R, Chang MC, Zimmerman AM, Zimmerman S. 1991. Reduction of the fertilizing capacity of sea urchin sperm by cannabinoids derived from marijuana. I. Inhibition of the acrosome reaction induced by egg jelly. *Molecular Reproduction and Development* 29:51–59.
136. Schuel H, Chang MC, Berkery D, Schuel R, Zimmerman AM, Zimmerman S. 1991. Cannabinoids inhibit fertilization in sea urchins by reducing the fertilizing capacity of sperm. *Pharmacology, Biochemistry, and Behavior* 40:609–615.
137. Schuel H, Goldstein E, Mechoulam R, Zimmerman AM, Zimmerman S. 1994. Anandamide (arachidonyl ethanolamide), a brain cannabinoid receptor, agonist, reduces sperm fertilizing capacity in sea urchins by inhibiting the acrosome reaction. *Proceedings of the National Academy of Sciences* 91:7678–7682.
138. Sidney S, Beck JE, Tekawa IS, Quesenberry CP Jr, Friedman GD. 1997a. Marijuana use and mortality. *American Journal of Public Health* 87:585–590.
139. Sidney S, Quesenberry CP Jr, Friedman GD, Tekawa IS. 1997b. Marijuana use and cancer incidence (California, United States). *Cancer Cause and Control* 8:722–728.
140. Solowij N. 1995. Do cognitive impairments recover following cessation of cannabis use? *Life Sciences* 56:2119–2126.
141. Sridhar JS, Raub WA, Weatherby NL, et al. 1994. Possible role of marijuana smoking as a carcinogen in the development of lung cancer at a young age. *Journal of Psychoactive Drugs* 26:285–288.
142. Stenchever MA, Kunysz TJ, Allen MA. 1974. Chromosome breakage in users of marijuana. *American Journal of Gynecology* 118:106–113.
143. Stephens RS, Roffman RA, Simpson EE. 1993. Adult marijuana users seeking treatment. *Journal of Consulting and Clinical Psychology* 61:1100–1104.
144. Tanda G, Pontieri FE, Di Chiara G. 1997. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common $\mu 1$ opioid receptor mechanism. *Science* 276:2048–2049.
145. Tart CT. 1971. *On Being Stoned: A Psychological Study of Marijuana Intoxication*. Palo Alto, CA: Science and Behavior Books.
146. Tashkin DP, Coulson AH, Clark VA, Simmons M, Bourque LB, Duann S, Spivey GH, Gong H. 1987. Respiratory symptoms and lung function in habitual, heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. *American Review of Respiratory Disease* 135:209–216.
147. Tashkin DP, Simmons MS, Sherrill DL, Coulson AH. 1997. Heavy habitual marijuana smoking does not cause an accelerated decline in FEV₁ with age. *American Journal of Respiratory and Critical Care Medicine* 155:141–148.

148. Tashkin E. 1999. Effects of marijuana on the lung and its defenses against infection and cancer. *School Psychology International* 20:23–37.
149. Taylor FM. 1988. Marijuana as a potential respiratory tract carcinogen: A retrospective analysis. *Southern Medical Journal* 81:1213–1216.
150. Tennant FS. 1980. Histopathologic and clinical abnormalities of the respiratory system in chronic hashish smokers. *Substance and Alcohol Actions/Misuse* 1:93–100.
151. Thornicroft G. 1990. Cannabis and psychosis: Is there epidemiological evidence for an association? *British Journal of Psychiatry* 157:25–33.
152. Tindall B, Cooper D, Donovan B, Barnes T, Philpot C, Gold J, Penny R. 1988. The Sydney AIDS Project: Development of acquired immunodeficiency syndrome in a group of HIV seropositive homosexual men. *Australian and New Zealand Journal of Medicine* 18:8–15.
153. Tsou K, Patrick SL, Walker JM. 1995. Physical withdrawal in rats tolerant to delta-9-tetrahydrocannabinol precipitated by a cannabinoid receptor antagonist. *European Journal of Pharmacology* 280:R13–R15.
154. Van Hoozen BE, Cross CE. 1997. Respiratory tract effects of marijuana. *Clinical Reviews in Allergy and Immunology* 15:243–269.
155. Volkow ND, Gillespie H, Mullani N, Tancredi L, Grant C, Valentine A, Hollister L. 1996. Brain glucose metabolism in chronic marijuana users at baseline and during marijuana intoxication. *Psychiatry Research* 67:29–38.
156. Wagner JA, Varga K, Kunos G. 1998. Cardiovascular actions of cannabinoids and their generation during shock. *Journal of Molecular Medicine* 76:824–836.
157. Wallace JM, Tashkin DP, Oishi JS, Barbers RG. 1988. Peripheral blood lymphocyte subpopulations and mitogen responsiveness in tobacco and marijuana smokers. *Journal of Psychoactive Drugs* 20:9–14.
158. Wehner FC, Van Rensburg SJ, Theil PF. 1980. Mutagenicity of marijuana and transkei tobacco smoke condensates in the salmonella/microsome assay. *Mutation Research* 77:135–142.
159. Wenger T, Croix D, Tramu G, Leonardelli J. 1992. Effects of delta-9-tetrahydrocannabinol on pregnancy, puberty, and the neuroendocrine system. In: Murphy L, Bartke A, Editors, *Marijuana/Cannabinoids: Neurobiology and Neurophysiology*. Boca Raton, FL: CRC Press.
160. White SC, Brin SC, Janicki BW. 1975. Mitogen-induced blastogenic responses of lymphocytes from marijuana smokers. *Science* 188:71–72.
161. Whitfield RM, Bechtel LM, Starich GH. 1997. The impact of ethanol and marinol/marijuana usage on HIV+/ AIDS patients undergoing azidothymidine, azidothymidine/dideoxycytidine, ordideoxyinosine therapy. *Alcoholism Clinical and Experimental Research* 21:122–127.
162. Wu TC, Tashkin DP, Djahed B, Rose JE. 1988. Pulmonary hazards of smoking marijuana as compared with tobacco. *New England Journal of Medicine* 318:347–351.
163. Yesavage JA, Leirer VO, Denari M, Hollister LE. 1985. Carry-over effects of marijuana intoxication on aircraft pilot performance: A preliminary report. *American Journal of Psychiatry* 142:1325–1329.
164. Zuckerman B, Frank DA, Hingson R, Amaro H, Levenson S, Kayne J, Parker S, Vinci R, Aboagye K, Fried L, Cabral J, Timperi R, Bauchner H. 1989. Effects of maternal marijuana and cocaine use on fetal growth. *New England Journal of Medicine* 320:762–768.

4

The Medical Value of Marijuana and Related Substances



During the course of drug development, a typical compound is found to have some medical benefit and then extensive tests are undertaken to determine its safety and proper dosage for medical use. In contrast, marijuana has been widely used in the United States for decades.¹⁶² In 1996, 68.6 million people—32% of the U.S. population over 12 years old—had tried marijuana or hashish at least once; 5% were current users.¹⁶²

The data on the adverse effects of marijuana are more extensive than the data on its effectiveness. Clinical studies of marijuana are difficult to conduct: researchers interested in clinical studies of marijuana face a series of barriers, research funds are limited, and there is a daunting thicket of regulations to be negotiated at the federal level (those of the Food and Drug Administration, FDA, and the Drug Enforcement Agency, DEA) and state levels (see chapter 5). Consequently, the rapid growth in basic research on cannabinoids contrasts with the paucity of substantial clinical studies on medical uses.

This chapter is devoted to an analysis of the therapeutic value of marijuana and cannabinoids for specific symptoms associated with various conditions. The risks associated with the medical use of marijuana are discussed in chapter 3. It should be noted that THC, the primary active ingredient in marijuana, is an FDA-approved drug referred to as dronabinol and marketed as Marinol. Marijuana is advocated primarily for relief from the symptoms of disease rather than as a cure.

For the most part, the logical categories for the medical use of mari-

juana are not based on particular diseases but on symptoms—such as nausea, appetite loss, or chronic pain—each of which can be caused by various diseases or even by treatments for diseases. This chapter is therefore organized by symptoms rather than by diseases. There are eight sections. The first section explains clinical trials, the following five deal with specific symptoms and conditions, and the last two summarize the medical benefits of marijuana and cannabinoids. The five sections on symptoms and conditions are as follows: pain, nausea and vomiting, wasting syndrome and appetite stimulation, neurological symptoms (including muscle spasticity), and glaucoma.

The Institute of Medicine (IOM) study team received reports of more than 30 different medical uses of marijuana, more than could be carefully reviewed in a report of this length; even more uses are reported elsewhere.^{62,63} For most of the infrequently mentioned medical uses of marijuana there are only a few anecdotal reports. This report reviews only the most prominent symptoms that are reportedly relieved by marijuana. However, many of those diseases not reviewed here share common symptoms, such as pain, nausea and vomiting, and muscle spasms, which might be relieved by cannabinoid drugs.

STANDARDS FOR EVALUATING CLINICAL TRIALS

Before evaluating individual clinical trials concerning the efficacy and safety of medical uses of marijuana and cannabinoids, it is useful to review the general qualities of clinical trials. Clinical trials involve groups of individuals in which different treatments are compared among different groups. Such trials measure the efficacy of a medication and are required by the FDA for approval of any new drug or new use of a drug (discussed further in chapter 5).

The degree of assurance that the outcome of a clinical trial is due to the treatment being tested depends on how well the trial is designed. Three important factors to consider in evaluating the design of a clinical trial are sample selection, subjective effects, and effects that are independent of the treatment. For *sample selection* it is important to ensure that patients are allocated to different treatment groups in such a way that the groups are not biased toward a particular treatment outcome. For example, the health status, gender, and ages of different treatment groups should be equivalent. *Subjective effects* must be controlled because they influence experimental results in two important ways. First, a patient's expectation that a treatment will be effective can influence the degree of its effect (for example, in the control of nausea). Second, the investigator's expectation can influence his or her interpretation of the treatment effect (for example, when assessing the level of pain experienced by a patient).

For these reasons, double blinding, in which neither the subject nor the person who assesses the drug's effect is aware of the subject's treatment group, is particularly important in cannabinoid drug studies. Another important control for subjective effects includes the use of placebo drugs, which are inert substances, or the use of comparison drugs that have effects similar to the experimental drug. Finally, the quality of the experimental design depends on controlling for factors that are unrelated to the test drug but that might nonetheless influence the treatment outcome. *Sequencing effects* are one example of such factors. For example, patients might react differently to the same medication depending on whether the medication was administered after an effective or an ineffective treatment. Likewise, a patient whose symptoms are initially mild might react differently to a drug than would a patient whose symptoms are initially severe. Because psychological effects are associated with cannabinoid drugs, it is important to consider how such side effects might influence the therapeutic value of the treatment. Conditions such as pain and nausea are especially susceptible to subjective influences. For example, depending on the person, THC can reduce or increase anxiety; it is important to determine to what extent this "side effect" contributes to the therapeutic effect.

While double-blind, randomized, controlled clinical trials offer the highest degree of assurance of drug efficacy, such trials are not always feasible. Vulnerable populations, such as children, older patients, and women of child-bearing age, are often excluded from experimental drug trials for safety reasons. Nonetheless, such patients are part of everyday clinical practice. The challenge of integrating the ideal of standardized and rigorous processes for treatment evaluation with everyday clinical practice has encouraged interest in single-patient trials.⁶⁷ Methods for such trials have been established and tested in a variety of clinical settings, usually under everyday conditions.^{66,105,159} They are particularly valuable when physicians or patients are uncertain about the efficacy of treatment for symptomatic diseases. Controls can be incorporated even in this kind of trial. Such trials can be double blinded and can involve cross-over designs in which the patient is treated with alternating treatments, such as placebo-drug-placebo or one drug followed by another drug. As with any other clinical trial, a single-patient trial should be designed to permit objective comparison between treatments.

ANALGESIA

Pain is the most common symptom for which patients seek medical assistance.⁵ Pain associated with structural or psychophysiological disorders can arise from somatic, visceral, or neural structures. *Somatic pain* results from activation of receptors outside the brain and is transmitted to

the brain via peripheral nerves. *Visceral pain* results from activation of specific pain receptors in the intestine (visceral nociceptive receptors); it is characterized as a deep aching or cramping sensation, but its source is often experienced at sites remote from the site of receptor activation, a phenomenon known as referred pain. *Neuropathic pain* results from injury to peripheral receptors, nerves, or the central nervous system; it is typically burning, the skin feels abnormally unpleasant when gently touched (dysesthesia), and it often occurs in an area of sensory loss, as in the case of postherpetic neuralgia (shingles).

All of the currently available analgesic (pain-relieving) drugs have limited efficacy for some types of pain. Some are limited by dose-related side effects and some by the development of tolerance or dependence. A cannabinoid, or other analgesic, could potentially be useful under any of the following circumstances:

- There is a medical condition for which it is more effective than any currently available medication.
- It has a broad clinical spectrum of efficacy and a unique side effect profile.
- It has synergistic interactions with other analgesics.
- It exhibits “side effects” that are considered useful in some clinical situations.
- Its efficacy is enhanced in patients who have developed tolerance to opioids.

There have not been extensive clinical studies of the analgesic potency of cannabinoids, but the available data from animal studies indicate that cannabinoids could be useful analgesics. In general, cannabinoids seem to be mild to moderate analgesics. Opiates, such as morphine and codeine, are the most widely used drugs for the treatment of acute pain, but they are not consistently effective in chronic pain; they often induce nausea and sedation, and tolerance occurs in some patients. Recent research has made it clear that CB₁ receptor agonists act on pathways that partially overlap with those activated by opioids but through pharmacologically distinct mechanisms (see chapter 2). Therefore, they would probably have a different side effect profile and perhaps additive or synergistic analgesic efficacy.

In light of the evidence that cannabinoids can reduce pain in animals, it is important to re-evaluate the evidence of analgesic efficacy in humans and to ask what clinical evidence is needed to decide whether cannabinoids have any use in the treatment of pain.

Clinical Studies of Cannabinoids

There have been three kinds of studies of the effects of cannabinoids on pain in human volunteers: studies of experimentally induced acute pain, studies of postsurgical acute pain, and studies of chronic pain. Overall, there have been very few studies—only one since 1981—and they have been inconclusive.

Experimentally Induced Acute Pain

Early studies of cannabinoids on volunteers did not demonstrate consistent analgesia when experimental pain models were used. In fact, three early volunteer studies of THC and experimental pain caused by a variety of pain modalities—electrical stimulation, tourniquet pain, and thermal pain—resulted in an *increase* in pain sensitivity (hyperalgesia).^{22,84,108}

Other studies also failed to show an analgesic effect of THC, but they were not well designed. Raft and co-workers found no evidence of THC effect on pain thresholds and pain tolerance following electrical stimulation and noxious pressure.¹⁵⁰ But their study suffers from two major methodological problems. First, they measured only the extremes of pain sensation—*threshold* (the lowest intensity at which a particular stimulus is perceived as painful) and *tolerance* (the maximum intensity of pain that a subject can withstand). However, most pain is experienced in an intermediate range, where effects on pain suppression are most detectable. Modern methods of pain assessment in humans typically use ratings of the intensity of the sensation of pain; those methods are superior to assessing the effects of a drug on the extremes of pain.¹⁹² Second, Raft and co-workers did not include a positive control; that is, they did not demonstrate the adequacy of their method by showing that an established analgesic, such as an opiate or narcotic, was effective under their study conditions.

Clark and co-workers²² tested the effect of smoked marijuana on thermal pain in volunteers and failed to observe an analgesic effect. However, because of the study design, the results are inconclusive. First, there was no positive control to demonstrate the adequacy of their methods; second, the study subjects were habitual marijuana users. During the study, they were hospitalized and allowed free access to marijuana cigarettes for a period of four weeks, consuming an average of four to 17 marijuana cigarettes per day. Pain was tested “approximately every one to two weeks.” Thus, it is quite likely that the subjects were tolerant to THC at the time of testing.

Surgical Acute Pain

Raft and co-workers¹⁵⁰ found no analgesic effect of THC on surgical pain induced by tooth extraction. However, that study suffered from several serious limitations: the tooth extraction included treatment with the local anesthetic lidocaine, the pain during the procedure was assessed 24 hours later, and there was no positive control. Levonantradol (a synthetic THC analogue) was tested in 56 patients who had moderate to severe postoperative or trauma pain.⁸⁹ They were given intramuscular injections of levonantradol or placebo 24 hours after surgery. To control for previous drug exposure, patients with a history of drug abuse or addiction and those who received an analgesic, antiinflammatory, tranquilizer, sedative, or anesthetic agent within 24 hours of the test drug were excluded from the study. On average, pain relief was significantly greater in the levonantradol-treated patients than in the placebo-treated patients. Because the authors did not report the number or percentage of people who responded, it is not clear whether the average represents consistent pain relief in all levonantradol-treated patients or whether some people experienced great relief and a few experienced none.

Chronic Pain

The most encouraging clinical data on the effects of cannabinoids on chronic pain are from three studies of cancer pain. Cancer pain can be due to inflammation, mechanical invasion of bone or other pain-sensitive structure, or nerve injury. It is severe, persistent, and often resistant to treatment with opioids. In one study, Noyes and co-workers found that oral doses of THC in the range of 5–20 mg produced analgesia in patients with cancer pain.^{139,140} The first experiment was a double-blind, placebo-controlled study of 10 subjects and measured both pain intensity and pain relief.¹⁴⁰ Each subject received all drug treatments: placebo and 5, 10, 15, and 20 mg of THC in pill form; each pill was identical in appearance and given on successive days. The 15- and 20-mg doses of THC produced significant analgesia. There were no reports of nausea or vomiting. In fact, at least half the patients reported increased appetite. With a 20-mg dose of THC, patients were heavily sedated and exhibited “depersonalization,” characterized by a state of dreamy immobility, a sense of unreality, and disconnected thoughts. Five of 36 patients exhibited adverse reactions (extreme anxiety) and were eliminated from the study. Only one patient experienced this effect at the 10-mg dose of THC. The mean age of the patients was 51 years, and they were probably not experienced marijuana smokers. A limitation of this study is that there were no positive con-

trols—that is, other analgesics that could provide a better measure of the degree of analgesia produced by THC.

In a later larger single-dose study, the same investigators reported that the analgesic effect of 10 mg of THC was equivalent to that of 60 mg of codeine; the effect of 20 mg of THC was equivalent to that of 120 mg of codeine.¹³⁹ (Note that codeine is a relatively weak analgesic.) The side effect profiles were similar, though THC was more sedating than codeine. In a separate publication the same authors published data indicating that patients had improved mood, a sense of well-being, and less anxiety.¹³⁹

The results of the studies mentioned above on cancer pain are consistent with the results of using a nitrogen analogue of THC. Two trials were reported: one compared this analogue with codeine in 30 patients, and a second compared it with placebo or secobarbital, a short-acting barbiturate.¹⁷⁵ For mild, moderate, and severe pain, the THC analogue was equivalent to 50 mg of codeine and superior to placebo and to 50 mg of secobarbital.

Case Reports and Surveys

The few case reports of clinical analgesia trials of cannabinoids are not convincing.^{85,120} There are, however, anecdotal surveys that raise the possibility of a role for cannabinoids in some patients who have chronic pain with prominent spasticity. A recent survey of over 100 patients with multiple sclerosis reported that a large number obtained relief from spasticity and limb pain (discussed further under the section on multiple sclerosis).²⁸ Several said that it relieved their phantom pain and headache.⁴¹

Migraine Headaches

There is clearly a need for improved migraine medications. Sumatriptan (Imitrex) is the best available medication for migraine headaches, but it fails to abolish migraine symptoms in about 30% of migraine patients.^{118,147} Marijuana has been proposed numerous times as a treatment for migraine headaches, but there are almost no clinical data on the use of marijuana or cannabinoids for migraine. Our search of the literature since 1975 yielded only one scientific publication on the subject. It presents three cases of cessation of daily marijuana smoking followed by migraine attacks—not convincing evidence that marijuana relieves migraine headaches.⁴³ The same result could have been found if migraine headaches were a consequence of marijuana withdrawal. While there is no evidence that marijuana withdrawal is followed by migraines, when analyzing the strength of reports such as these it is important to consider

all logical possibilities. Various people have claimed that marijuana relieves their migraine headaches, but at this stage there are no conclusive clinical data or published surveys about the effect of cannabinoids on migraine.

However, a possible link between cannabinoids and migraine is suggested by the abundance of cannabinoid receptors in the periaqueductal gray (PAG) region of the brain. The PAG region is part of the neural system that suppresses pain and is thought to be involved in the generation of migraine headaches.⁵² The link or lack thereof between cannabinoids and migraine might be elucidated by examining the effects of cannabinoids on the PAG region.¹¹⁰ Recent results indicating that both cannabinoid receptor subtypes are involved in controlling peripheral pain¹⁵ suggest that the link is possible. Further research is warranted.

Conclusions: Analgesia

A key question to address is whether there is any receptor selectivity for the analgesic efficacy of cannabinoids. Are the unwanted side effects (amnesia and sedation) caused by the same receptors in the same brain regions as those producing the analgesia? If the answer is *yes*, enhancing efficacy will not solve the problem of sedation. Similarly, are the pleasant side effects due to an action at the same receptor? Can the feelings of well-being and appetite stimulation be separated by molecular design? Recent results indicating that both cannabinoid receptor subtypes are independently involved in controlling peripheral pain¹⁵ (discussed in chapter 2) strongly suggest that this is possible and that further research is warranted.

Further research into the basic circuitry underlying cannabinoid analgesia should be valuable. The variety of neural pathways that underlie the control of pain suggests that a synergistic analgesia “cocktail” would be effective. For example, Lichtman and Martin have shown the involvement of an $\alpha 2$ adrenoceptor in cannabinoid analgesia.¹¹¹ Perhaps a combination of a CB₁ agonist and an $\alpha 2$ agonist (such as clonidine) would provide enhanced analgesia with less severe side effects.

Clinical studies should be directed at pain patients for whom there is a demonstrated need for improved management and where the particular side effect profile of cannabinoids promises a clear benefit over current approaches. The following patient groups should be targeted for clinical studies of cannabinoids in the treatment of pain:

- Chemotherapy patients, especially those being treated for the mucositis, nausea, and anorexia.

- Postoperative pain patients (using cannabinoids as an opioid adjunct to determine whether nausea and vomiting from opioids are reduced).
- Patients with spinal cord injury, peripheral neuropathic pain, or central poststroke pain.
- Patients with chronic pain and insomnia.
- AIDS patients with cachexia, AIDS neuropathy, or any significant pain problem.

In any patient group an essential question to be addressed is whether the analgesic efficacy of opioids can be augmented. The strategy would be to find the ceiling analgesic effect with an opioid (as determined by pain intensity and tolerability of side effects) and then add a cannabinoid to determine whether additional pain relief can be obtained. That would begin the investigation of potential drug combinations. As with any clinical study on analgesic drugs, it will be important to investigate the development of tolerance and physical dependence; these are not themselves reasons to exclude the use of cannabinoids as analgesics, but such information is essential to the management of many drugs that are associated with tolerance or physical dependence.

A secondary question would be whether THC is the only or the best component of marijuana for analgesia. How does the analgesic effect of the plant extract compare with that of THC alone? If there is a difference, it will be important to identify the combinations of cannabinoids that are the most effective analgesics.

In conclusion, the available evidence from animal and human studies indicates that cannabinoids can have a substantial analgesic effect. One exception is the lack of analgesic effect in studies on experimentally induced acute pain, but because of limitations in the design of those studies they were inconclusive. Further clinical work is warranted to establish the magnitude of the effect in different clinical conditions and to determine whether the effect is sustained. Although the usefulness of cannabinoids appears to be limited by side effects, notably sedation, other effects such as anxiolysis, appetite stimulation, and perhaps antinausea and antispasticity effects should be studied in randomized, controlled clinical trials. These very "special" effects might warrant development of cannabinoid drugs for particular clinical populations.

NAUSEA AND VOMITING

Nausea and vomiting (emesis) occur under a variety of conditions, such as acute viral illness, cancer, radiation exposure, cancer chemotherapy, postoperative recovery, pregnancy, motion, and poisoning. Both

are produced by excitation of one or a combination of triggers in the gastrointestinal tract, brain stem, and higher brain centers (Figure 4.1, Emesis-stimulating pathways).¹²⁷ There are numerous cannabinoid receptors in the nucleus of the solitary tract, a brain center that is important in the control of emesis.^{79,80} Although the same mechanisms appear to be involved in triggering both nausea and vomiting, either can occur without the other. Much more is known about the neural mechanisms that produce vomiting than about those that produce nausea, in large part because vomiting is a complex behavior involving coordinated changes in the gastrointestinal tract, respiratory muscles, and posture, whereas nausea is a sensation involving primarily higher brain centers and lacks a discrete observable action.^{104,128} Most reports on the antiemetic effects of marijuana or cannabinoids are based on chemotherapy-induced emesis; they are the subject of the following section.

Chemotherapy-Induced Nausea and Vomiting

The use of effective chemotherapeutic drugs has produced cures in some malignancies and retarded the growth of others, but nausea and

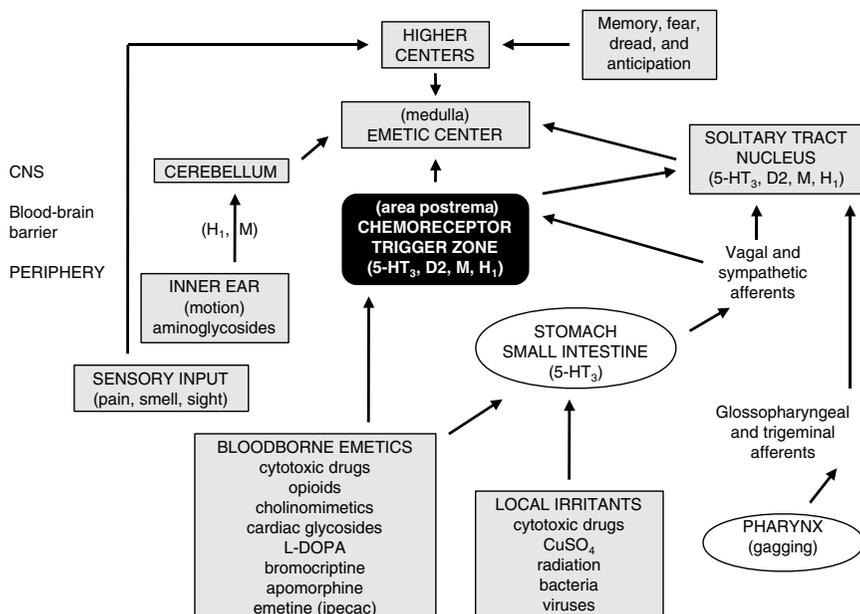


FIGURE 4.1 Emesis-stimulating pathways. SOURCE: Bruton, L.L. 1996. P. 929 in Hardman et al., eds., *The Pharmacological Basis of Therapeutics*, 9th edition. New York: McGraw-Hill. Reprinted with permission.

vomiting are frequent side effects of these drugs. Nausea ranks behind only hair loss as a concern of patients on chemotherapy, and many patients experience it as the worst side effect of chemotherapy. The side effects can be so devastating that patients abandon therapy or suffer diminished quality of life. As a result, the development of effective strategies to control the emesis induced by many chemotherapeutic agents is a major goal in the supportive care of patients with malignancies.

The mechanism by which chemotherapy induces vomiting is not completely understood. Studies suggest that emesis is caused by stimulation of receptors in the central nervous system or the gastrointestinal tract. This stimulation appears to be caused by the drug itself, a metabolite of the drug, or a neurotransmitter.^{6,12,35} In contrast with an emetic like apomorphine, there is a delay between the administration of chemotherapy and the onset of emesis. This delay depends on the chemotherapeutic agent; emesis can begin anywhere from a few minutes after the administration of an agent like mustine to an hour for cisplatin.¹²

The most desirable effect of an antiemetic is to control emesis completely, which is currently the primary standard in testing new antiemetic agents (R. Gralla, IOM workshop). Patients recall the number of emetic episodes accurately, even if their antiemetics are sedating or affect memory;¹⁰¹ thus, the desired end point of complete control is also a highly reliable method of evaluation. The degree of nausea can be estimated through the use of established visual analogue scales.^{*21,55,101}

Another consideration in using antiemetic drugs is that the frequency of emesis varies from one chemotherapeutic agent to another. For example, cisplatin causes vomiting in more than 99% of patients who are not taking an antiemetic (with about 10 vomiting episodes per dose), whereas methotrexate causes emesis in less than 10% of patients.^{55,82,83} Among chemotherapeutic agents, cisplatin is the most consistent emetic known and has become the benchmark for judging antiemetic efficacy. Antiemetics that are effective with cisplatin are at least as effective with other chemotherapeutic agents. Controlling for the influence of prior chemotherapy and balancing predisposing factors such as, sex, age, and prior heavy alcohol use among study groups are vital for reliability. Reliable randomization of patients and blinding techniques (easier when there are no psychoactive effects) are also necessary to evaluate the control of vomiting and nausea.

*The *visual analogue scale* is a continuous line representing all possible levels of a particular sensation. It is an estimation of a patient's subjective evaluation and not a true measurement. Patients select a point anywhere on the line to demonstrate the level of sensation they are experiencing, with one end representing one extreme, such as no sensations, and the other end representing the opposite extreme, such as a maximum level of that sensation.

THC and Marijuana Therapy for Chemotherapy-Induced Nausea and Vomiting

Cannabinoids are mildly effective in preventing emesis in some patients who are receiving cancer chemotherapy. Several cannabinoids have been tested as antiemetics, including THC (both Δ^9 -THC and Δ^8 -THC) and the synthetic cannabinoids nabilone and levonantradol. Smoked marijuana has also been examined.

Antiemetic Properties of THC

The quality and usefulness of antiemetic studies depend on adherence to the methodological considerations outlined above. Many of the reported clinical experiences with cannabinoids are not based on definitive experimental methods. In studies that compared THC with a placebo, THC was usually found to possess antiemetic properties. However, the chemotherapeutic drug varied in most trials, and some studies included small numbers of patients. In one study THC was found to be superior to a placebo in patients receiving methotrexate, an agent that is not a strong emetic.¹⁸ When the same investigators studied THC in a small number of patients who were receiving a chemotherapeutic drug that is more likely to cause emesis than anthracycline, the antiemetic effect was poor.¹⁹

Other trials were designed to compare THC with that of Compazine (prochlorperazine).^{143,160} In the 1980s, prochlorperazine was one of the more effective antiemetics available, but it was not completely satisfactory, and the search for better agents continued. THC and prochlorperazine given orally showed similar degrees of efficacy, but the studies often used various chemotherapeutic agents. Even when administered in combination, THC and prochlorperazine failed to stop vomiting in two-thirds of patients.⁵⁰

In a carefully controlled double-blind study comparing THC with the antiemetic drug metoclopramide, in which no patient had previously received chemotherapy and in which anticipatory emesis was therefore not a factor, all patients received the same dose of cisplatin and were randomly assigned to the THC group or the metoclopramide group. Complete control of emesis occurred in 47% of those treated with metoclopramide and 13% of those treated with THC.⁵⁸ Major control (two or fewer episodes) occurred in 73% of the patients given metoclopramide compared to 27% of those given THC. There were many flaws in experimental methods, but those results suggest that THC has some, but not great, efficacy in reducing chemotherapy-induced emesis.^{18,19,50,161} The studies also indicate that the degree of efficacy is not high. In 1985, the

FDA approved THC in the form of dronabinol for this treatment (discussed in chapter 5).

The THC metabolite, 11-OH-THC, is more psychoactive than THC but is a weaker antiemetic.¹²¹ Thus, it might be possible to design antiemetic cannabinoids without the psychological effects associated with marijuana or THC. Δ^8 -THC is less psychoactive than THC¹⁵¹ but was found to completely block both acute and delayed chemotherapy-induced emesis in a study of eight children, ages 3–13 years.* Two hours before the start of each cancer treatment and every six hours thereafter for 24 hours, the children were given Δ^8 -THC as oil drops on the tongue or in a bite of bread (18 mg/m² body surface area). The children received a total of 480 treatments. The only side effects reported were slight irritability in two of the youngest children (3.5 and 4 years old). Based on the prediction that the THC-induced anxiety effects would be less in children than in adults, the authors used doses that were higher than those recommended for adults (5–10 mg/m² body surface area).

Antiemetic Properties of Synthetic THC Analogues

Nabilone (Cesamet) and levonantradol were tested in various settings; the results were similar to those with THC. Efficacy was observed in several trials, but no advantage emerged for these agents.^{176,185} As in the THC trials, nabilone and levonantradol reduced emesis but not as well as other available agents in moderately to highly emetogenic settings. Neither is commercially available in the United States.

Antiemetic Properties of Marijuana

Among the efforts to study marijuana was a preliminary study conducted in New York state on 56 cancer patients who were unresponsive to conventional antiemetic agents.¹⁸⁸ The patients were asked to rate the effectiveness of marijuana compared with results during prior chemotherapy cycles. In this survey, 34% of patients rated marijuana as moderately or highly effective. The authors concluded that marijuana had antiemetic efficacy, but its relative value was difficult to determine because no control group was used and the patients varied with respect to previous experiences, such as marijuana use and THC therapy.

*Note that the authors of this study chose to use Δ^8 -THC because it is more stable and easier to produce than Δ^9 -THC; it does not follow from this particular study that marijuana, with its mixture of cannabinoids, should be a more powerful antiemetic than Δ^9 -THC.

A Canadian oncology group conducted a double-blind, cross-over, placebo-controlled study comparing smoked marijuana with THC in pill form in 20 patients who were receiving various chemotherapeutic drugs.¹⁰⁷ The degree of emetic control was similar: only 25% of patients achieved complete control of emesis; 35% of the patients indicated a slight preference for the THC pills over marijuana, 20% preferred marijuana, and 45% expressed no preference.¹⁰⁷

Neither study showed a clear advantage for smoked marijuana over oral THC, but neither reported data on the time course of antiemetic control, possible advantages of self-titration with the smoked marijuana, or the degree to which patients were able to swallow the pills. Patients with severe vomiting would have been unlikely to be able to swallow or keep the pills down long enough for them to take effect. The onset of drug effect is much faster with inhaled or injected THC than it is for oral delivery.^{87,112,141} Although many marijuana users have claimed that smoked marijuana is a more effective antiemetic than oral THC, no controlled studies have yet been published that analyze this in sufficient detail to estimate the extent to which this is the case.

Side Effects Associated with THC and Marijuana in Antiemetic Therapy

Frequent side effects associated with THC or marijuana are dizziness, dry mouth, hypotension, moderate sedation, and euphoria or dysphoria.^{18,19,50,107,143,160,176,185} To patients, dry mouth and sedation are the least troubling side effects. Perhaps the most troubling side effects are orthostatic hypotension and dizziness, which could increase the patient's distress.

There is disagreement as to whether the psychoactive effects of THC correlate with its antiemetic activity. In the prospective double-blind trial comparing THC with metoclopramide, the authors reported no relationship between the occurrence of complete antiemetic control and euphoria or dysphoria.⁵⁸ Other investigators believe that the occurrence of euphoria or dysphoria is often associated with improved antiemetic control.¹⁶⁰ Nevertheless, there is a consensus among investigators that dysphoric effects are more common among patients who have had no prior experience with cannabinoids. An important and unexpected problem encountered in the New York state open trial with marijuana was the inability of nearly one-fourth of the patients to tolerate the administration of marijuana by smoking.¹⁸⁸ The intolerance could have been due to inexperience with smoking marijuana and is an important consideration.

Therapy for Chemotherapy-Induced Nausea and Vomiting

Present Therapy

New classes of antiemetics that have emerged over the past 10 years have dramatically reduced the nausea and vomiting associated with cancer chemotherapy and transformed the acceptance of cisplatin by cancer patients. The new antiemetics—including selective serotonin type 3 receptor antagonists, substituted benzamides, corticosteroids, butyrophenones, and phenothiazines—have few side effects when given over a short term and are convenient in various clinical settings.

The most effective commonly used antiemetics are serotonin receptor antagonists (ondansetron and granisetron) with or without corticosteroids.^{37,56,88,145,155} In a combination trial of dexamethasone (a corticosteroid) and a serotonin antagonist, complete control of acute cisplatin-induced emesis was observed in about 75% of patients. If the chemotherapy was only moderately emetogenic, up to 90% of the patients who received the combination achieved complete control of emesis. Side effects of those antiemetic agents include headache, constipation, and alterations in liver function, but they are generally well tolerated by most patients.¹³

Other commonly used antiemetics are phenothiazines—prochlorperazine (Compazine) and haloperidol—and metoclopramide. Metoclopramide is somewhat less effective than the serotonin antagonists and has more side effects, including acute dystonic reactions, drowsiness, diarrhea, and depression.^{13,37} Side effects associated with phenothiazines are severe or acute dystonic reactions, hypotension, blurred vision, drowsiness, dry mouth, urinary retention, allergic reactions, and occasional jaundice.¹³

The cost of effective antiemetic regimens can vary markedly, depending on the agent, dose, schedule, and route of administration. Overall, oral regimens cost less than intravenous regimens because of lower pharmacy and administration costs, as well as lower acquisition costs in many countries. Regimens with a cost to the pharmacy as low as about \$30 to \$35 per treatment session have been shown to be effective;⁵⁷ these costs are for treatment of acute emesis and delayed emesis with generic agents where available.

Although it is generally not well known by the public, major progress in controlling chemotherapy-induced acute nausea and vomiting has been made since the 1970s. Patients receiving the most difficult to control emetic agents now have no more than about a 20–30% likelihood of experiencing acute emesis,¹⁵⁵ whereas in the 1970s the likelihood was nearly 100% despite antiemetics.^{55,86} As has been seen, most antiemetic studies with

BOX 4.1

Attitudes of Oncologists Toward Prescribing Marijuana

In the 1990s, two groups of investigators conducted three surveys on the attitudes of clinical oncologists toward prescribing marijuana as an antiemetic. These studies are arguably out of date in that the antiemetics available now are much more effective than those available when the studies were conducted. Nonetheless, the studies merit attention because they are still often cited as evidence for or against the use of marijuana as an antiemetic.

The two groups' results were contradictory. In 1994, by which time serotonin receptor antagonists (5-HT receptors) had become available, Schwartz and Beveridge¹⁷¹ concluded that oncologists had little interest in prescribing marijuana to control emesis, whereas Doblin and Kleiman³⁹ had concluded in 1991 that interest was great. Since 1994, the two groups have debated in the literature as to which study represents the true sentiment among oncologists.^{38,172,177} In fact, numerous methodological differences between the two studies might explain the different results.^{38,172} Ultimately, these studies are irrelevant. Both deal with perceptions rather than pharmacological realities based on well-designed outcome studies.¹⁷⁷

cannabinoids had methodological difficulties and are inconclusive. The evidence from the well-conducted trials indicate that cannabinoids reduce emesis in about one-fourth of patients receiving cancer chemotherapy. Cannabinoids are not as effective as several other classes of agents, such as substituted benzamides, serotonin receptor antagonists, and corticosteroids. The side effects associated with cannabinoid use are generally tolerable. Like cannabinoids, smoked marijuana, was apparently effective, but the efficacy was no greater than that of available antiemetic agents now considered to be marginally satisfactory. At present, the most effective antiemetic regimens are combinations of oral serotonin receptor antagonists with dexamethasone in single-dose regimens given before chemotherapy. Neither multiple-dose regimens nor intravenous antiemetics provide better control, and both add unnecessary costs.^{59,81}

Future Therapy

Advances in therapy for chemotherapy-induced nausea and vomiting will require discovery of agents that work through mechanisms dif-

ferent from those of existing antiemetics, including the serotonin antagonists. Among the proposed new pathways, neurokinin-1 (NK-1) receptor antagonists appear to be the most promising. Neurokinin receptors are found in brain and intestine and are thought to be involved in motor activity, mood, pain and reinforcement. They might well be involved in mediating intestinal sensations, including nausea. In animal models, agents that block the NK-1 receptor prevent cisplatin-induced emesis. At the time of this writing, clinical trials with NK-1 receptor antagonists were under way (phase II or small phase III comparison studies). Preliminary results indicated that these agents have useful activity in both acute and delayed chemotherapy-induced emesis (that is, beginning or persisting 24 or more hours after chemotherapy) and are safe to administer orally.^{102,135}

It is theoretically possible, considering that the mechanism of cannabinoid action appears to differ from that of the serotonin receptor antagonists and of corticosteroids, that THC added to more effective regimens might enhance control of emesis. Such combinations should aim to be as convenient as possible and have few additional side effects. The critical issue is not whether marijuana or cannabinoid drugs might be superior to the new drugs, but whether some group of patients might obtain added or better relief from marijuana or cannabinoid drugs.

Even with the best antiemetic drugs, the control of nausea and vomiting that begins or persists 24 hours after chemotherapy remains imperfect. The pathophysiology of delayed emesis appears different from that of acute emesis, and it is more likely to occur with a strong emetic agent, but it varies from patient to patient. Treatment to prevent this emesis requires dosing both before and after chemotherapy.¹⁰³

Conclusions: Chemotherapy-Induced Nausea

Most chemotherapy patients are unlikely to want to use marijuana or THC as an antiemetic. In 1999, there are more effective antiemetic agents available than were available earlier. By comparison, cannabinoids are only modest antiemetics. However, because modern antiemetics probably act through different mechanisms, cannabinoids might be effective in people who respond poorly to currently used antiemetic drugs, or cannabinoids might be more effective in combination with a new drug than is either alone. For both reasons, studies of the effects of adjunctive cannabinoids on chemotherapy-induced emesis are worth pursuing for patients whose emesis is not optimally controlled with other agents.

While some people who spoke to the IOM study team described the mood-enhancing and anxiety-reducing effects of marijuana as a positive contribution to the antiemetic effects of marijuana, one-fourth of the

patients in the New York state study described earlier were unable to tolerate smoked marijuana. Overall, the effects of oral THC and smoked marijuana are similar, but there are differences. For example, in the residential studies of experienced marijuana users by Haney and co-workers, subjects reported that marijuana made them feel "mellow,"⁷¹ whereas comparable doses of oral THC did not.⁷⁰ Such differences might be due to the different routes of delivery of THC, as well as the different mixture of cannabinoids found in the marijuana plant. As of this writing, no studies had been published that weighed the relative contributions of those different factors.

The goal of antiemetic medications is to prevent nausea and vomiting. Hence, antiemetics are typically given before chemotherapy, in which case a pill is an effective form of drug delivery. However, in patients already experiencing severe nausea or vomiting, pills are generally ineffective because of the difficulty in swallowing or keeping a pill down and slow onset of the drug effect. Thus, an inhalation (but preferably not smoking) cannabinoid drug delivery system would be advantageous for treating chemotherapy-induced nausea.

Until the development of rapid-onset antiemetic drug delivery systems, there will likely remain a subpopulation of patients for whom standard antiemetic therapy is ineffective and who suffer from debilitating emesis. It is possible that the harmful effects of smoking marijuana for a limited period of time might be outweighed by the antiemetic benefits of marijuana, at least for patients for whom standard antiemetic therapy is ineffective and who suffer from debilitating emesis. Such patients should be evaluated on a case-by-case basis and treated under close medical supervision.

WASTING SYNDROME AND APPETITE STIMULATION

Wasting syndrome in acquired immune deficiency syndrome (AIDS) patients is defined by the Centers for Disease Control and Prevention as the involuntary loss of more than 10% of baseline average body weight in the presence of diarrhea or fever of more than 30 days that is not attributable to other disease processes.¹⁷ Anorexia (loss of appetite) can accelerate wasting by limiting the intake of nutrients. Wasting (cachexia) and anorexia are common end-stage features of some fatal diseases, such as AIDS, and of some types of metastatic cancers. In AIDS, weight loss of as little as 5% is associated with decreased survival, and a body weight about one-third below ideal body weight results in death.^{99,158}

There are two forms of malnutrition: starvation and cachexia. Starvation, the deprivation of essential nutrients, results from famine or poverty, malabsorption, eating disorders such as anorexia nervosa, and so on. Star-

vation leads to metabolic adaptations that deplete body fat before losses of lean tissue. Cachexia results from tissue injury, infection, or tumor and is characterized by a disproportionate loss of lean body mass, such as skeletal muscle. The effects of starvation regardless of the cause can usually be reversed by providing food, whereas the effects of cachexia can be reversed only through control of the underlying disease and—at least for some patients—drugs that stimulate metabolism, such as growth hormone or androgenic-anabolic hormones.

Malnutrition in HIV-Infected Patients

By 1997 more than 30 million people worldwide were infected with human immunodeficiency virus (HIV), and the number is predicted to increase to almost 40 million by the year 2000.^{126,186} Malnutrition is common among AIDS patients and plays an independent and important role in their prognosis.^{95,100,158} Because treatment for malnutrition depends on whether it is caused by starvation or cachexia, one needs to know the effects of HIV infection on metabolic processes. The answer depends on the clinical situation and can be either or both.⁹⁴

The development of malnutrition in HIV infection has many facets. Malnutrition in HIV-infected patients results in a disproportionate depletion of body cell mass,* total body nitrogen, and skeletal muscle mass; all are consistent with cachexia.^{97,194} Body composition studies show that the depletion of body cell mass precedes the progression to AIDS (falling CD4 lymphocyte counts); this suggests that malnutrition is a consequence of the inflammatory response to the underlying viral infection, rather than a general complication of AIDS.¹⁴⁴ In contrast, weight loss is often episodic and related to acute complications, such as febrile opportunistic infections.¹¹³ Mechanisms underlying wasting in HIV-infected patients depend on the stage of HIV infection and on specific associated complications.

The many reasons for decreased food intake among AIDS patients include mouth, throat, or esophageal infections or ulcers (oropharyngeal and esophageal pathology); adverse effects of medications;¹⁹⁶ diarrhea; enteric infection; malabsorption; serious systemic infection; focal or diffuse neurological disease; HIV enteropathy; depression; fatigue; and poverty. Nutrient malabsorption is often the result of microorganism overgrowth or infection in the intestine, especially in the later stages of AIDS.^{95,157}

*Body cell mass is the fat-free cellular mass. It is composed of the cells of the muscle and organs, plus circulating hematopoietic cells and the aqueous compartment of adipocytes. It is not fat, extracellular water, or extracellular solids (such as tendons).

Marijuana and THC for Malnutrition in HIV-Infected Patients

Despite their frequency of use, little has been published about the effectiveness of marijuana or cannabinoids for the treatment of malnutrition and wasting syndrome in HIV-infected patients. The only cannabinoid evaluated in controlled clinical studies is THC, or dronabinol. Short-term (six-week) and long-term (one-year) therapy with dronabinol was associated with an increase in appetite and stable weight, and in a previous short-term (five-week) clinical trial in five patients, dronabinol was shown to increase body fat by 1%.^{8,9,179} In 1992, the FDA approved THC, under the trade name Marinol (dronabinol), as an appetite stimulant for the treatment of AIDS-related weight loss. Megestrol acetate (Megace) is a synthetic derivative of progesterone that can stimulate appetite and cause substantial weight gain when given in high doses (320–640 mg/day) to AIDS patients. Megestrol acetate is more effective than dronabinol in stimulating weight gain, and dronabinol has no additive effect when used in combination with megestrol acetate.¹⁸³ HIV/AIDS patients are the largest group of patients who use dronabinol. However, some reject it because of the intensity of neuropsychological effects, an inability to titrate the oral dose easily, and the delayed onset and prolonged duration of its action.³ There is evidence that cannabinoids modulate the immune system (see chapter 2, “Cannabinoids and the Immune System”), and this could be a problem in immunologically compromised patients. No published studies have formally evaluated use of any of the other cannabinoids for appetite stimulation in wasting.

Anecdotes abound that smoked marijuana is useful for the treatment of HIV-associated anorexia and weight loss.^{23,62} Some people report a preference for smoked marijuana over oral THC because it gives them the ability to titrate the effects, which depend on how much they inhale. In controlled laboratory studies of healthy adults, smoked marijuana was shown to increase body weight, appetite, and food intake.^{47,119} Unfortunately, there have been no controlled studies of the effect of smoked marijuana on appetite, weight gain, and body composition in AIDS patients. At the time of this writing, Donald Abrams, of the University of California, San Francisco, was conducting the first clinical trial to test the safety of smoked marijuana in AIDS patients, and the results were not yet available.

A major concern with marijuana smoking in HIV-infected patients is that they might be more vulnerable than other marijuana users to immunosuppressive effects of marijuana or to the exposure of infectious organisms associated marijuana plant material (see chapter 3, “Marijuana Smoke”).

Therapy for Wasting Syndrome in HIV-Infected Patients

Present Therapy

Generally, therapy for wasting in HIV-infected people focuses on appetite stimulation. Few therapies have proved successful in treatment of the AIDS wasting syndrome. The stimulant studied most is megestrol acetate, which has been shown to increase food intake by about 30% over baseline for reasons that remain unknown. Its effect in producing substantial weight gain is dose dependent, but most of the weight gained is in fat tissue, not lean body mass. Although the findings are still preliminary, anabolic compounds, such as testosterone or growth hormone, might be useful in preventing the loss of or in restoring lean body mass in AIDS patients.^{10,44,64,170} Enteral and parenteral nutrition have also been evaluated and shown to increase weight, but again the increase is due more to body fat than to lean body mass.^{96,98}

Encouraging advances in the antiviral treatment of HIV infection and developments in the prophylaxis of and therapy for opportunistic infections have recently changed the outlook for the long-term health of HIV-infected people. Death rates have been halved, and the frequency of serious complications, including malnutrition, has fallen markedly.^{94,133}

Future Therapy

The primary focus of future therapies for wasting in HIV-infected patients is to increase lean body mass as well as appetite. Active systemic infections are associated with profound anorexia, which is believed to be mediated by cytokines that stimulate inflammation through their actions in and outside the brain.¹³² Cytokine inhibitors, such as thalidomide, have been under investigation as potential treatments to increase lean body mass and reduce malnutrition. Even though cannabinoids do not appear to restore lean body mass, they might be useful as adjunctive therapy. For example, cannabinoids could be used as appetite stimulants, in patients with diminished appetite who are undergoing resistance exercises or anabolic therapy to increase lean body mass. They could also be beneficial for a variety of effects, such as increased appetite, while reducing the nausea and vomiting caused by protease inhibitors and the pain and anxiety associated with AIDS.

Considering current knowledge about malnutrition in HIV infection, cannabinoids, by themselves, will probably not constitute primary therapy for this condition but might be useful in combination with other therapies, such as anabolic agents. Specifically, the proposed mechanism of action of increasing food intake would most likely be ineffective in pro-

moting an increase in skeletal muscle mass and functional capacity—the goal in the treatment of cachexia in AIDS patients.

Malnutrition in Cancer Patients

Malnutrition compromises the quality of life of many cancer patients and contributes to the progression of their disease. About 30% of Americans will develop cancer in their lifetimes, and two-thirds of those who get cancer will die as a result of it.⁵ Depending on the type of cancer, 50–80% of patients will develop cachexia and up to 50% of them will die, in part, as a result of cachexia.^{11,40} The cachexia appears to result from the tumor itself, and cytokines (proteins secreted by the host during an immune response to tumor) are probably important factors in this development. Cachexia does not occur in all cancer patients, but generally occurs in the late stages of advanced cancer of the pancreas, lung, and prostate.

The only cannabinoid evaluated for treating cachexia in cancer patients is dronabinol, which has been shown to improve appetite and promote weight gain.⁵⁴ Present treatments for cancer cachexia are similar to that for cachexia in AIDS patients. These treatments are usually indicated in late stages of advanced disease and include megestrol acetate and enteral and parenteral nutrition. Megestrol acetate stimulates appetite and promotes weight gain in cancer patients, although the gain is mostly in fat mass (reviewed by Bruera 1998¹⁴). Both megestrol acetate and dronabinol have dose-related side effects that can be troublesome for patients: megestrol acetate can cause hyperglycemia and hypertension, and dronabinol can cause dizziness and lethargy. Cannabinoids have also been shown to modulate the immune system (see chapter 2, “Cannabinoids and the Immune System”), and this could be contraindicated in some cancer patients (both the chemotherapy and the cancer can be immunosuppressive).

Future treatments will probably depend on the development of methods that block cytokine actions and the use of selective β_2 -adrenergic receptor agonists to increase muscle mass.^{14,73} Treatments for cancer cachexia will also most likely need to identify individual patients' needs. Some patients might need only a cytokine inhibitor, whereas others could benefit from combined approaches, such as an appetite stimulant and β_2 -adrenergic receptor agonists. In this respect, such cannabinoids as THC might prove useful as part of a combination therapy as an appetite stimulant, antiemetic, analgesic, and anxiolytic, especially for patients in late stages of the disease.

Anorexia Nervosa

Anorexia nervosa, a psychiatric disorder characterized by distorted body image and self-starvation, affects an estimated 0.6% of the U.S. population, with a greater prevalence in females than males.⁵ Its mortality is high, and response to standard treatments is poor.

THC appears to be ineffective in treating this disease. In one study it caused severe dysphoric reactions in three of 11 patients.⁶⁵ One possible explanation of the dysphoria is that THC increases appetite and thus intensifies the mental conflict between hunger and food refusal.¹³ Furthermore, such patients might have underlying psychiatric disorders, such as schizophrenia and depression, in which cannabinoids might be hazardous (see chapter 3, "Psychological Harms").

Current treatments include psychological techniques to overcome emotional or behavioral problems and dietary intervention to reverse the malnutrition.¹⁹⁵ Pharmacological treatments, such as antidepressants, have been used in addition to psychotherapy but tend to lack the desired level of efficacy.³³ Recently, alterations in a gene for one of the serotonin receptors have been identified in some patients with anorexia nervosa.⁴⁵ The possibility of a genetic component suggests a pathway for the development of new drugs to treat this disease.

Conclusions: Wasting Syndrome and Appetite Stimulation

The profile of cannabinoid drug effects suggests that they are promising for treating wasting syndrome in AIDS patients. Nausea, appetite loss, pain, and anxiety are all afflictions of wasting, and all can be mitigated by marijuana. Although some medications are more effective than marijuana for these problems, they are not equally effective in all patients. A rapid-onset (that is, acting within minutes) delivery system should be developed and tested in such patients. Smoking marijuana is not recommended. The long-term harm caused by smoking marijuana makes it a poor drug delivery system, particularly for patients with chronic illnesses.

Terminal cancer patients pose different issues. For those patients the medical harm associated with smoking is of little consequence. For terminal patients suffering debilitating pain or nausea and for whom all indicated medications have failed to provide relief, the medical benefits of smoked marijuana might outweigh the harm.

NEUROLOGICAL DISORDERS

Neurological disorders affect the brain, spinal cord, or peripheral nerves and muscles in the body. Marijuana has been proposed most often

as a source of relief for three general types of neurological disorders: muscle spasticity, particularly in multiple sclerosis patients and spinal cord injury victims; movement disorders, such as Parkinson's disease, Huntington's disease, and Tourette's syndrome; and epilepsy. Marijuana is not proposed as a cure for such disorders, but it might relieve some associated symptoms.

Muscle Spasticity

Spasticity is the increased resistance to passive stretch of muscles and increased deep tendon reflexes. Muscles may also contract involuntarily (flexor and extensor spasms). In some cases these contractions are debilitating and painful and require therapy to relieve the spasms and associated pain.

There are numerous anecdotal reports that marijuana can relieve the spasticity associated with multiple sclerosis or spinal cord injury, and animal studies have shown that cannabinoids affect motor areas in the brain—areas that might influence spasticity.^{51,78,130,168}

Multiple Sclerosis

Multiple sclerosis (MS) is a condition in which multiple areas of the central nervous system (CNS) are affected. Many nerve fibers become demyelinated, some are destroyed, and scars (sclerosis) form, resulting in plaques scattered throughout the white matter of the CNS. (Myelin is the lipid covering that surrounds nerve cell fibers and facilitates the conduction of signals along nerve cells and ultimately between the brain, the spinal cord, and the rest of the body.) MS exacerbations appear to be caused by abnormal immune activity that causes inflammation and myelin destruction in the brain (primarily in the periventricular area), brain stem, or spinal cord. Demyelination slows or blocks transmission of nerve impulses and results in an array of symptoms such as fatigue, depression, spasticity, ataxia (inability to control voluntary muscular movements), vertigo, blindness, and incontinence. About 90% of MS patients eventually develop spasticity. There are an estimated 2.5 million MS patients worldwide, and spasticity is a major concern of many patients and physicians.¹³⁴ Spasticity is variably experienced as muscle stiffness, muscle spasms, flexor spasms or cramps, muscle pain or ache. The tendency for the legs to spasm at night (flexor spasms) can interfere with sleep.

Marijuana is often reported to reduce the muscle spasticity associated with MS.^{62,123} In a mail survey of 112 MS patients who regularly use marijuana, patients reported that spasticity was improved and the associated pain and clonus decreased.²⁸⁷ However, a double-blind placebo-controlled

study of postural responses in 10 MS patients and 10 healthy volunteers indicated that marijuana smoking impaired posture and balance in both MS patients and the volunteers.⁶¹ Nevertheless, the 10 MS patients felt that they were clinically improved. The subjective improvement, while intriguing, does not constitute unequivocal evidence that marijuana relieves spasticity. Survey data do not measure the degree of placebo effect, estimated to be as great as 30 percent in pain treatments.^{122,131} Furthermore, surveys do not separate the effects of marijuana or cannabinoids on mood and anxiety from the effects on spasticity.

The effects of THC on spasticity were evaluated in a series of three clinical trials testing a total of 30 patients.^{24,148,187} They were "open trials," meaning that the patients were informed before treatment that they would be receiving THC. Based on patient report or clinical exam by the investigator, spasticity was less severe after the THC treatment. However, THC was not effective in all patients and frequently caused unpleasant side effects. Spasticity was also reported to be less severe in a single case study after nabilone treatment (Figure 4.2).¹¹⁷

In general, the abundant anecdotal reports are not well supported by the clinical data summarized in Table 4.1. But this is due more to the limitation of the studies than to negative results. There are no supporting animal data to encourage clinical research in this area, but there also are no good animal models of the spasticity of MS. Without an appropriate model, studies to determine the physiological basis for how marijuana or THC might relieve spasticity cannot be conducted. Nonetheless, the survey results suggest that it would be useful to investigate the potential therapeutic value of cannabinoids in relieving symptoms associated with MS. Such research would require the use of objective measures of spasticity, such as the pendulum test.* Since THC is mildly sedating, it is also important to distinguish this effect from antispasticity effects in any such investigations. Mild sedatives, such as Benadryl or benzodiazepines, would be useful controls for studies on the ability of cannabinoids to relieve muscle spasticity. The regular use of smoked marijuana, however, would be contraindicated in a chronic condition like MS.

Spinal Cord Injury

In 1990, there were about 15 million patients worldwide with spinal cord injury, and an estimated 10,000 new cases are reported each year in

*The *pendulum test* is an objective and accurate measure of MS-induced spasticity. It is done by videotaping a patient who lies supine on a table with his or her leg extending off the edge. The leg is dropped and the resulting motion is mathematically analyzed by computer to provide a quantitative measure of spasticity.

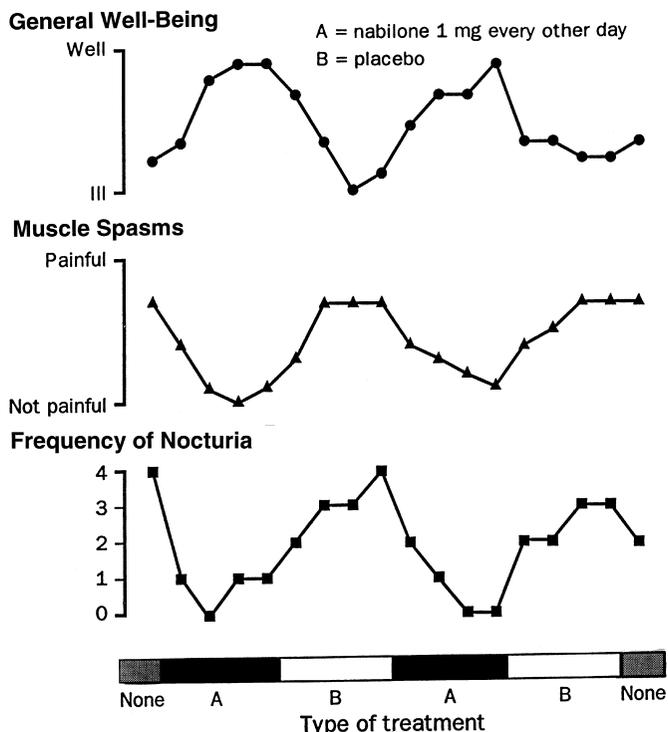


FIGURE 4.2 Effect of nabilone on multiple sclerosis symptoms. This figure shows the results of a trial in which a 45-year-old man with MS was given four-week treatments alternately with placebo and nabilone. The patient served as both experimental subject and control; his treatment sequence was nabilone-placebo-nabilone-placebo. That pattern of alternating treatments reduces the possibility that the observed changes are unrelated to the drug and are not simply due to other factors that changed with time. The results of the trial are consistent with the possibility that THC might relieve spasticity, but although more rigorous than many self-report studies of psychoactive substances, it has problems. First, the patient could not distinguish the treatments at the time of taking them, but after the nabilone treatment he felt sedated. Thus, it is not possible to know how much the expectation of relief contributed to his perception of relief. Second, the study measured his perception of pain, in which spasticity is an important factor but not the only factor. It is not possible to know the extent to which the perception of pain was affected by nabilone and how much by the stimulus that generated the pain—in this case, involuntary muscle contractions. Because it is unaffected by conscious control, the frequency of nocturia is clearer evidence of the effect of THC, although it might also represent how well the patient slept. This trial with a single person is intriguing but not definitive proof that THC can reliably relieve spasticity. SOURCE: Martyn et al. (1995).¹¹⁷ Reprinted with permission.

TABLE 4.1 Studies on the Effects of Marijuana and Cannabinoids in Multiple Sclerosis

Drug and Dose	Study Design	Results	Reference
Marijuana	Mail survey 112/233 MS patients	Survey was mailed to 233 MS patients, of whom 112 (48%) responded; 97% of respondents reported improved spasticity and reduced pain.	Consroe and co-workers (1997) ²⁸
Marijuana	Clinical trial 1 MS patient	Reduction in spasticity and improved ataxia.	Meinck and co-workers (1989) ¹²³
Marijuana	Double-blind, placebo-controlled 10 MS patients; 10 normal individuals	MS patients felt they were improved, but posture and balance were impaired.	Greenberg and co-workers (1994) ⁶¹
Oral THC 5–15 mg every 6 hrs, up to 18 hrs	Open trial 8 MS patients	5 patients experienced subjective but not objective improvement in motor coordination; objective improvement in tremor demonstrated in 2 of the 8 patients.	Clifford (1983) ²⁴
Oral THC 5 and 10 mg, single doses	Double-blind, placebo controlled 9 MS patients	Spasticity was improved based on examiner ratings.	Petro and Ellenberger (1981) ¹⁴⁸
Oral THC 2.5–15 mg, once or twice daily for 5 days	Double-blind, placebo controlled, crossover 13 MS patients	Patients reported subjective decreases in spasticity at doses of 7.5 mg or greater, but no changes in objective measures of spasticity or weakness were observed.	Ungerleider and co-workers (1987) ¹⁸⁷
Nabilone (THC analogue)	Placebo-controlled 1 MS patient	The patient reported increased well-being, less frequent nocturia, and reduced severity of muscle spasticity during nabilone treatment (Figure 4.2).	Martyn and co-workers (1995) ¹¹⁷

the United States alone.^{134,138} About 60% of spinal cord injuries occur in people younger than 35 years old. Most will need long-term care and some lifelong care.¹¹⁶

Many spinal cord injury patients report that marijuana reduces their muscle spasms.¹¹⁴ Twenty-two of 43 respondents to a 1982 survey of

people with spinal cord injuries reported that marijuana reduced their spasticity.¹¹⁴ One double-blind study of a paraplegic patient with painful spasms in both legs suggested that oral THC was superior to codeine in reducing muscle spasms.^{72,120} Victims of spinal cord injury reporting at IOM workshops noted that smoking marijuana reduces their muscle spasms, their nausea, and the frequency of their sleepless nights. The caveats described for surveys of spasticity relief in MS patients also apply here.

Therapy for Muscle Spasticity

Present Therapy. Present therapy for spasticity includes the various medications listed in Table 4.2. Baclofen and tizanidine, the most commonly prescribed antispasticity drugs, relieve spasticity and spasms with various degrees of success. The benefit of these agents is generally only partial. Their use is complicated by the side effects of drowsiness, dry mouth, and increased weakness.

Future Therapy. The discovery of agents that work through mechanisms different from those of existing antispasticity drugs will be an important advance in the treatment of spasticity. The aim of new treatments will be to relieve muscle spasticity and pain without substantially increasing muscle weakness in conditions that result in spasticity. The treatment for MS itself will likely be directed at immunomodulation. Various immunomodulating agents, such as beta-interferon and glatiramer acetate, have been shown to reduce the frequency of symptomatic attacks, the progression of disability, and the rate of appearance of demyelinated lesions as detected by magnetic resonance imaging.⁵

Conclusion: Muscle Spasticity

Basic animal studies described in chapter 2 have shown that cannabinoid receptors are particularly abundant in areas of the brain that control

TABLE 4.2 Classes of Antispasticity Drugs

Drug Class	Drug
GABA _B -receptor agonists	Baclofen
α-Receptor agonists	Tizanidine
Noncompetitive GABA _A -receptor agonists	Benzodiazepines, including diazepam
Calcium blockers in skeletal muscle	Dantrolene

movement and that cannabinoids affect movement and posture in animals as well as humans. The observations are consistent with the possibility that cannabinoids have antispastic effects, but they do not offer any direct evidence that cannabinoids affect spasticity, even in animals. The available clinical data are too meager to either accept or dismiss the suggestion that marijuana or cannabinoids relieve muscle spasticity. But the few positive reports of the ability of THC and related compounds to reduce spasticity, together with the prevalence of anecdotal reports of the relief provided by marijuana, suggest that carefully designed clinical trials testing the effects of cannabinoids on muscle spasticity should be considered (see chapter 1).^{25,62} Such trials should be designed to assess the degree to which the anxiolytic effects of cannabinoids contribute to any observed antispastic effects.

Spasticity occurring at night can be very disruptive to sleep. Thus, a long-lasting medication would be especially useful for MS patients at bedtime—when drowsiness would be a beneficial rather than an unwanted side effect and mood-altering effects would be less of a problem. One caution is related to the effects of THC on the stages of sleep, which should be evaluated in MS patients who have sleep disturbances. If THC is proven to relieve spasticity, a pill might be the preferred route of delivery for nighttime use because of its long duration of action. Compared to the currently available therapies, the long half-life of THC might allow for a smoother drug effect throughout the day. The intensity of the symptoms resulting from spasticity, particularly in MS, can rapidly increase in an unpredictable fashion such that the patient develops an “attack” of intense muscle spasms lasting minutes to hours. An inhaled form of THC (if it were shown to be efficacious) might be appropriate for those patients.

Movement Disorders

Movement disorders are a group of neurological conditions caused by abnormalities in the basal ganglia and their subcortical connections through the thalamus with cortical motor areas. The brain dysfunctions ultimately result in abnormal skeletal muscle movements in the face, limbs, and trunk. The movement disorders most often considered for marijuana or cannabinoid therapy are dystonia, Huntington’s disease, Parkinson’s disease, and Tourette’s syndrome. Movement disorders are often transiently exacerbated by stress and activity and improved by factors that reduce stress. This is of particular interest because for many people marijuana reduces anxiety.

Dystonia

Dystonia can be a sign of other basal ganglion disorders, such as Huntington's disease and tardive dyskinesia (irreversible development of involuntary dyskinesic movements) and can be a primary basal ganglion disorder. Primary dystonias are a heterogeneous group of chronic slowly progressive neurological disorders characterized by dystonic movements—slow sustained involuntary muscle contractions that often result in abnormal postures of limbs, trunk, and neck. Dystonias can be confined to one part of the body, such as spasmodic torticollis (neck) or Meige's syndrome (facial muscles), or can affect many parts of the body, such as dystonia musculorum deformans.⁵ Dystonia can cause mild to severe disability and sometimes pain secondary to muscle aching or arthritis. Some dystonias are genetic; others are caused by drugs. The specific neuropathological changes in these diseases have not been determined.

No controlled study of marijuana in dystonic patients has been published, and the only study of cannabinoids was a preliminary open trial of cannabidiol (CBD) that suggested modest dose-related improvements in the five dystonic patients studied.³⁰ In mutant dystonic hamsters, however, the cannabinoid receptor agonist, WIN 55,212-2, can produce antidystonic effects.¹⁵³

Huntington's Disease

Huntington's disease is an inherited degenerative disease that usually appears in middle age and results in atrophy or loss of neurons in the caudate nucleus, putamen, and cerebral cortex. It is characterized by arrhythmic, rapid muscular contractions (chorea), emotional disturbance, and dementia (impairment in intellectual and social ability). Animal studies suggest that cannabinoids have antichoreic activity, presumably because of stimulation of CB₁ receptors in the basal ganglia.^{129,168}

On the basis of positive results in one of four Huntington's disease patients, CBD and a placebo were tested in a double-blind crossover study of 15 Huntington's disease patients who were not taking any antipsychotic drugs. Their symptoms neither improved nor worsened with CBD treatment.^{27,164}

The effects of other cannabinoids on patients with Huntington's disease are largely unknown. THC and other CB₁ agonists are more likely candidates than CBD, which does not bind to the CB₁ receptor. Those receptors are densely distributed on the very neurons that perish in Huntington's disease.¹⁵² Thus far there is little evidence to encourage clinical studies of cannabinoids in Huntington's disease.

Parkinson's Disease

Parkinson's disease, a degenerative disease, affects about 1 million Americans over the age of 50.⁵³ It is characterized by bradykinesia (slowness in movement), akinesia (abrupt stoppage of movement), resting tremor, muscular rigidity, and postural instability.

Theoretically, cannabinoids could be useful for treating Parkinson's disease patients because cannabinoid agonists specifically inhibit the pathways between the subthalamic nucleus and substantia nigra and probably also the pathways between the subthalamic nucleus and globus pallidus (these structures shown in Figure 2.6).^{165,169} The latter effect was not directly tested but is consistent with what is known about these neural pathways. Hyperactivity of the subthalamic neurons, observed in both Parkinson's patients and animal models of Parkinson's disease, is hypothesized to be a major factor in the debilitating bradykinesia associated with the disease.³⁶ Furthermore, although cannabinoids oppose the actions of dopamine in intact rats, they augment dopamine activation of movement in an animal model of Parkinson's disease. This suggests the potential for adjunctive therapy with cannabinoid agonists.^{165-167,169}

At the time of this writing, we could find only one published clinical trial of marijuana involving five cases of idiopathic Parkinson's disease.⁴⁸ That trial was prompted by a patient's report that smoking marijuana reduced tremor, but the investigators found no improvement in tremor after the five patients smoked marijuana—whereas all subjects benefited from the administration of standard medications for Parkinson's disease (levodopa and apomorphine).⁴⁸ Although new animal data might someday indicate a use for cannabinoids in treating Parkinson's disease, current data do not recommend clinical trials of cannabinoids in patients with Parkinson's disease.

Tourette's Syndrome

Tourette's syndrome usually begins in childhood and is characterized by motor and vocal tics (involuntary rapid repetitive movements or vocalizations). It has been suggested that the symptoms might be mediated by a reduction in the activity of limbic-basal ganglia-thalamocortical circuits (shown in Figure 2.4).⁴² These circuits, while not well understood, appear to be responsible for translating a person's intentions to move into actual movements. Damage to these structures leads to either involuntary increases in movement (as in Huntington's disease) or the inability to make voluntary movements (as in Parkinson's disease). The nature of the deficit in Tourette's syndrome is unknown.

No clear link has been established between symptoms of Tourette's

syndrome and cannabinoid sites or mechanism of action. Pimozide and haloperidol, two widely used treatments for Tourette's syndrome, inhibit effects mediated by the neurotransmitter dopamine, whereas cannabinoids can increase dopamine release.^{154,181} The physiological relevance, if any, of these two observations has not been established.

Clinical reports consist of four case histories indicating that marijuana use can reduce tics in Tourette's patients.^{75,163} In three of the four cases the investigators suggest that beneficial effects of marijuana might have been due to anxiety-reducing properties of marijuana rather than to a specific antitetic effect.¹⁶³

Therapy for Movement Disorders

Various drugs are available (Table 4.3) to treat the different movement disorders. Common side effects of many of these drugs are sedation, lethargy, school and work avoidance, social phobia, and increased risk of parkinsonism and tardive dyskinesia. With some of the medications, like those used for dystonia, efficacy is lacking in up to 50% of the patients. In addition to medications, surgical interventions, such as pallidotomy and neurosurgical transplantation of embryonic substantia nigra tissue into the patient's striatum, have been tried in Parkinson's disease patients. Surgery is generally palliative and is still considered to be in the developmental phase.

TABLE 4.3 Drugs Used to Treat Movement Disorders

Dystonia	Parkinson's disease
Benzodiazepines	Levodopa
Tetrabenazine	Carbidopa+levodopa combination
Intramuscular botulinum toxin	Amantadine
Anticholinergics	Bromocriptine
Baclofen	Pergolide
	Pramipexole
Huntington's disease	Ropinirole
Reserpine	Selegiline
Tetrabenazine	Trihexyphenidyl
Haloperidol	Benztropine
Tourette's syndrome tics	
Pimozide	
Clonidine	
Haloperidol	

Conclusion: Movement Disorders

The abundance of CB₁ receptors in basal ganglia and reports of animal studies showing the involvement of cannabinoids in the control of movement suggest that cannabinoids would be useful in treating movement disorders in humans. Marijuana or CB₁ receptor agonists might provide symptomatic relief of chorea, dystonia, some aspects of parkinsonism, and tics. However, clinical evidence is largely anecdotal; there have been no well-controlled studies of adequate numbers of patients. Furthermore, nonspecific effects might confound interpretation of results of studies. For example, the anxiolytic effects of cannabinoids might make patients feel that their condition is improved, despite the absence of measurable change in their condition.

Compared to the abundance of anecdotal reports concerning the beneficial effects of marijuana on muscle spasticity, there are relatively few claims that marijuana is useful for treating movement disorders. This might reflect a lack of effect or a lack of individuals with movement disorders who have tried marijuana. In any case, while there are a few isolated reports of individuals with movement disorders who report a benefit from marijuana, there are no published surveys indicating that a substantial percentage of patients with movement disorders find relief from marijuana. Existing studies involve too few patients from which to draw conclusions. The most promising reports involve symptomatic treatment of spasticity. If the reported neuroprotective effects of cannabinoids discussed in chapter 2 prove to be therapeutically useful, this could benefit patients with movement disorders, but without further data such a benefit is highly speculative. Since stress often transiently exacerbates movement disorders, it is reasonable to hypothesize that the anxiolytic effects of marijuana or cannabinoids might be beneficial to some patients with movement disorders. However, chronic marijuana smoking is a health risk that could increase the burden of chronic conditions, such as movement disorders.

Cannabinoids inhibit both major excitatory and inhibitory inputs to the basal ganglia. This suggests that a cannabinoid agonist could produce opposite effects on movement, depending on the type of transmission (excitatory or inhibitory) that is most active at the time of drug administration. This property could be used to design treatments in basal ganglia movement disorders, such as Parkinson's disease where either the excitatory subthalamic input becomes hyperactive or the inhibitory striatal input becomes hypoactive. The dose employed would be a major factor in the therapeutic uses of cannabinoids in movement disorders; low doses should be desirable, while higher doses could be expected to aggravate pathological conditions. Thus, there is a clear reason to recommend pre-

clinical studies; that is, animal studies to test the hypothesis that cannabinoids play an important role in movement disorders.

With the possible exception of multiple sclerosis, the evidence to recommend clinical trials of cannabinoids in movement disorders is relatively weak. Ideally, clinical studies would follow animal research that provided stronger evidence than is currently available on the potential therapeutic value of cannabinoids in the treatment of movement disorders. Unfortunately, there are no good animal models for these disorders. Thus, double-blind, placebo-controlled clinical trials of isolated cannabinoids that include controls for relevant side effects should be conducted. Such effects include anxiolytic and sedative effects, which might either mask or contribute to the potential therapeutic effects of cannabinoids.

Epilepsy

Epilepsy is a chronic seizure disorder that affects about 2 million Americans and 30 million people worldwide.¹⁵⁶ It is characterized by recurrent sudden attacks of altered consciousness, convulsions, or other motor activity. A seizure is the synchronized excitation of large groups of brain cells. These abnormal electrical events have a wide array of possible causes, including injury to the brain and chemical changes derived from metabolic faults of exposure to toxins.¹⁵⁶

Seizures are classified as partial (focal) or generalized. Partial seizures are associated with specific sensory, motor, or psychic aberrations that reflect the function of the part of the cerebral cortex from which the seizures arise. Generalized seizures are usually the result of pathological conditions of brain sites that project to widespread regions of the brain. Such pathology can produce petit mal seizures or major grand mal convulsions.

Cannabinoids in Epilepsy

There are anecdotal and individual case reports that marijuana controls seizures in epileptics (reviewed in a 1997 British Medical Association report¹³), but there is no solid evidence. While there are no studies indicating that either marijuana or THC worsen seizures, there is no scientific basis to justify such studies.

In the only known case-controlled study that was designed to evaluate illicit drug use and the risk of first seizure, Ng and co-workers¹³⁷ concluded that marijuana is a protective factor for first-time seizures in men but not women. Men who used marijuana reportedly had fewer first-time seizures than men who did not use marijuana. That report was based on a comparison of 308 patients who had been admitted to a hospital after

their first seizure with a control group of 294 patients. The control group was made up of patients who had not had seizures and were admitted for emergency surgery, such as surgery for appendicitis, intestinal obstruction, or acute cholecystitis. Compared to men who did not use marijuana, the odds ratio of first seizure for men who had used marijuana within 90 days of hospital admission was 0.36 (95% confidence interval = 0.18–0.74). An odds ratio of less than one is consistent with the suggestion that marijuana users are less likely to have seizures. The results for women were not statistically significant. However, this was a weak study. It did not include measures of health status prior to hospital admissions for the patients' serious conditions, and differences in their health status might have influenced their drug use rather than—as suggested by the authors—that differences in their drug use influenced their health.

The potential antiepileptic activity of CBD has been investigated but is not promising. Three controlled trials were conducted in which CBD was given orally to patients who had had generalized grand mal seizures or focal seizures (Table 4.4). Two of these studies were never published, but information about one was published in a letter to the *South African Medical Journal*, and the other was presented at the 1990 Marijuana International Conference on Cannabis and Cannabinoids.¹⁸⁴

TABLE 4.4 Clinical Trials of Cannabidiol (CBD) in Epileptics

Study Design	Results	Reference
Double-blind placebo-controlled trial 8 epileptic patients were given CBD at 200–300 mg/day in conjunction with standard antiepileptic therapies.	4 of 8 remained almost free of convulsions. Three of the 4 were partially improved for up to 4.5 months.	Cunha and co-workers ³⁴
Double-blind placebo-controlled study 12 epileptic patients were given CBD at 200–300 mg/day along with standard antiepileptic drugs.	CBD had no effect on seizure frequency.	Ames ⁴
Double-blind placebo-controlled, add-on crossover trial 10 epileptic patients were given CBD at 300 mg/day for 6 months.	CBD had no effect on seizures.	Trembly and Sherman, 1990 ¹⁸⁴ (reviewed in Consroe and Sandyk, 1992 ²⁹)
Open trial One patient was given CBD at 900–1,200 mg/day for 10 months.	Seizure frequency was reduced in the patient.	Trembly and Sherman, 1990 ¹⁸⁴ (reviewed in Consroe and Sandyk, 1992 ²⁹)

Even if CBD had antiepileptic properties, these studies were likely too small to demonstrate efficacy. Proving efficacy of anticonvulsants generally requires large numbers of patients followed for months because the frequency of seizures is highly variable and the response to therapy varies depending on seizure type.^{4,49}

Therapy for Epilepsy

Present Therapy. Standard pharmacotherapy for partial and generalized seizures, listed in Table 4.5, involves a variety of anticonvulsant drugs. These drugs suppress seizures completely in approximately 60% of patients who have chronic epilepsy and improve seizures in another 15% of patients. All of the anticonvulsants listed in Table 4.5 have side effects, some of the more common of which are drowsiness, mental slowing, ataxia, tremor, hair loss, increased appetite, headache, insomnia, and rash. Nevertheless, recurrent seizures are physically dangerous and emotionally devastating, and preventing them outweighs many undesirable side effects of anticonvulsant drugs.

Future Therapy. The goal of epilepsy treatment is to halt the seizures with minimal or no side effects and then to eradicate the cause. Most of the anticonvulsant research on cannabinoids was conducted before 1986. Since then, many new anticonvulsants have been introduced and cannabinoid receptors have been discovered. At present, the only biological evidence of antiepileptic properties of cannabinoids is that CB₁ receptors are abundant in the hippocampus and amygdala. Both regions are involved in partial seizures but are better known for their role in functions unrelated to seizures.²⁶ Basic research might reveal stronger links between cannabinoids and seizure activity, but this is not likely to be as fruitful a

TABLE 4.5 Anticonvulsant Drugs for Various Types of Seizures

Generalized grand mal seizures	Partial (focal) seizures
Carbamazepine	Carbamazepine
Valproate	Phenytoin
Phenytoin	Valproate
Phenobarbital	Phenobarbital
	Clonazepam
Generalized petit mal seizures	Gabapentin
Ethosuximide	Lamotrigine
Clonazepam	Tiagabine (as adjunct therapy)
Valproate	

SOURCE: Adapted from Andreoli et al. (1997).⁵

subject of cannabinoid research as others. Given the present state of knowledge, clinical studies of cannabinoids in epileptics are not indicated.

Alzheimer's Disease

Food refusal is a common problem in patients who suffer from Alzheimer's type dementia. The causes of anorexia in demented people are not known but may be a symptom of depression. Antidepressants improve eating in some but not all patients with severe dementia. Eleven Alzheimer's patients were treated for 12 weeks on an alternating schedule of dronabinol and placebo (six weeks of each treatment). The dronabinol treatment resulted in substantial weight gains and declines in disturbed behavior.¹⁹⁰ No serious side effects were observed. One patient had a seizure and was removed from the study, but the seizure was not necessarily caused by dronabinol. Recurrent seizures without any precipitating events occur in 20% of patients who have advanced dementia of Alzheimer's type.¹⁸⁹ Nevertheless, these results are encouraging enough to recommend further clinical research with cannabinoids.

The patients in the study discussed above were in long-term institutional care, and most were severely demented with impaired memory. Although short-term memory loss is a common side effect of THC in healthy patients, it was not a concern in this study. However, the effect of dronabinol on memory in Alzheimer's patients who are not as severely disturbed as those in the above study would be an important consideration.

GLAUCOMA

After cataracts, glaucoma is the second-leading cause of blindness in the world; almost 67 million people are expected to be affected worldwide by the year 2000¹⁴⁹ (for an excellent review, see Alward, 1998²). The most common form of glaucoma, primary open-angle glaucoma (POAG), is a slowly progressive disorder that results in loss of retinal ganglion cells and degeneration of the optic nerve, causing deterioration of the visual fields and ultimately blindness. The mechanisms behind the disease are not understood, but three major risk factors are known: age, race, and high intraocular pressure (IOP). POAG is most prevalent among the elderly, with 1% affected in those over 60 years old and more than 9% in those over 80. In African Americans over 80, there is more than a 10% chance of having the disease, and older African Caribbeans (who are less racially mixed than African Americans) have a 20–25% chance of having the disease.¹⁰⁶

The eye's rigid shape is normally maintained in part by IOP, which is

regulated by the circulation of a clear fluid, the aqueous humor,* between the front of the lens and the back of the cornea. Because of impaired outflow of aqueous humor from the anterior chamber of the eye, a high IOP is a risk factor for glaucoma, but the mechanism by which it damages the optic nerve and retinal ganglion cells remains unclear.¹⁷⁴ The two leading possibilities are that high IOP interferes with nutrient blood flow to the region of the optic nerve or that it interferes with transport of nutrients, growth factors, and other compounds within the optic nerve axon (P. Kaufman, IOM workshop). If the interference continues, the retinal ganglion cells and optic nerve will permanently atrophy; the result is blindness.⁶⁸ Because high IOP is the only known major risk factor that can be controlled, most treatments have been designed to reduce it. However, reducing it does not always arrest or slow the progression of visual loss.^{20,109}

Marijuana and Cannabinoids in Glaucoma

Marijuana and THC have been shown to reduce IOP by an average of 24% in people with normal IOP who have visual-field changes. In a number of studies of healthy adults and glaucoma patients, IOP was reduced by an average of 25% after smoking a marijuana cigarette that contained approximately 2% THC—a reduction as good as that observed with most other medications available today.^{1,16,32,76,77,125,193} Similar responses have been observed when marijuana was eaten or THC was given in pill form (10–40 mg) to healthy adults or glaucoma patients.^{76,91} But the effect lasts only about three to four hours. Elevated IOP is a chronic condition and must be controlled continuously.

Intravenous administration of Δ^9 -THC, Δ^8 -THC, or 11-OH-THC to healthy adults substantially decreased IOP, whereas cannabiol, CBD, and β -OH-THC had little effect.^{31,146} The cause for the reduction in IOP remains unknown, but the effect appears to be independent of the frequently observed drop in arterial systolic blood pressure (Keith Green, Medical College of Georgia, personal communication).

Three synthetic cannabinoids were investigated; BW29Y, BW146Y, and nabilone. They were given orally to patients who had high IOP. BW146Y and nabilone were as effective as ingesting THC or smoking

*The cornea and lens must be optically clear, which means that there cannot be blood circulation in these tissues. The aqueous humor is a clear fluid that functions as alternative circulation across the rear of the cornea and to the lens, providing nutrients and removing waste from these tissues.

marijuana but again with a very short duration of action; BW29Y was ineffective.^{136,182}

Topical treatments with cannabinoids have been ineffective in reducing IOP. When Δ^9 -THC was applied topically as eye drops, whether once or four times a day, there was no decrease in IOP.^{60,90} Suspensions of lipophilic THC tended to be irritating to the eye.

In summary, cannabinoids and marijuana can reduce IOP when administered orally, intravenously, or by inhalation but not when administered topically. Even though a reduction in IOP by standard medications or surgery clearly slows the rate of glaucoma symptom progression, there is no direct evidence of benefits of cannabinoids or marijuana in the natural progression of glaucoma, visual acuity, or optic nerve atrophy.^{92,115}

In addition to lowering IOP, marijuana reduces blood pressure and has many psychological effects. Merritt and co-workers reported hypotension, palpitations, and psychotropic effects in glaucoma patients after inhalation of marijuana.¹²⁵ Cooler and Gregg³¹ also reported increased anxiety and tachycardia after intravenous infusion of THC (1.5–3 mg). All those side effects are problematic, particularly for elderly glaucoma patients who have cardiovascular or cerebrovascular disease. The reduction in blood pressure can be substantial and might adversely affect blood flow to the optic nerve.¹²⁴ Many people with systemic hypertension have their blood pressure reduced to manageable and acceptable levels through medication, but this does not seem to affect their IOP. In contrast, there is evidence that reduction in blood pressure to considerably below-normal levels influences IOP and ocular blood flow.^{46,74,142} Hence, in the case of an eye with high IOP or an optic nerve in poor condition and susceptibility to high IOP, reduced blood flow to the optic nerve could compromise a functional retina and be a factor in the progression of glaucoma.

Because it is not known how these compounds work, it is also not known how they might interact with other drugs used to treat glaucoma. If the mechanism involves a final common pathway, the effects of cannabinoids might not be additive and might even interfere with effective drugs.

Therapy for Glaucoma

Present Therapy

Six classes of drugs are used to treat glaucoma; all reduce IOP (Table 4.6).⁹³ In the late 1970s, when early reports of the effects of marijuana on IOP surfaced, only cholinomimetics, epinephrine, and oral carbonic anhydrase inhibitors were available. They are not popular today because of their side effects, such as pupil constriction or dilation, brow ache, tachycardia, and diuresis; all of them have been superseded by the other classes

TABLE 4.6 Classes of Drugs Used to Treat Glaucoma

Cholinergic agonists Pilocarpine	α_2-Adrenergic agonists Apraclonidine Brimonidine
β_2-Adrenergic agonists Epinephrine Dipivefrin	Carbonic anhydrase inhibitors Acetazolamide Dorzolamide (Trusopt)
β_2-Adrenergic antagonists Timolol Betaxolol (Betoptic)	Prostaglandin-F_{2a} analogues Latanoprost Unoprostone

of drugs.⁹³ Surgical options are also available today to lower IOP, including laser trabeculoplasty, trabeculectomy/sclerostomy, drainage implantation, and cyclodestruction of fluid-forming tissues.¹⁷³ Thus, there are now many effective options to slow the progression of glaucoma by reducing IOP.

One important factor in slowing the progression of glaucoma via medications that reduce IOP is patient compliance with dosing regimens. With respect to compliance, the ideal glaucoma drug is one that is applied at most twice a day (P. Kaufman, IOM workshop). If the dose must be repeated every three to four hours, patient compliance becomes a problem; for this reason, marijuana and the cannabinoids studied thus far would not be highly satisfactory treatments for glaucoma. Present therapies, especially combinations of approved topical drugs, can control IOP when administered once or twice a day, at a cost of about \$60 per month.

Future Therapy

In all likelihood the next generation of glaucoma therapies will deal with neural protection, neural rescue, neural regeneration, or blood flow, and the optic nerve and neural retina will be treated directly rather than just by lowering IOP (P. Kaufman, IOM workshop). There is some evidence that a synthetic cannabinoid, HU-211, might have neuroprotective effects *in vitro*; this presents a potential approach that has nothing to do with IOP.¹⁹⁷ HU-211 is commonly referred to as a cannabinoid because its chemical structure is similar to THC; however, it does not bind to cannabinoid receptor.

It is known that cannabinoids lower IOP fairly substantially but not how. No one has tested whether the effect is receptor mediated (B. Martin, IOM workshop). To do so, one could test whether a receptor antagonist

blocked the effects of THC or other cannabinoids. If the decrease were shown to be receptor mediated, it would be important to know whether it was through CB₁, which mediates central nervous system effects, or CB₂, which is not involved in CNS effects. If it were CB₂, it might be possible to reduce IOP without the CNS side effects. Finally, it is not known whether the endogenous cannabinoid system is a natural regulator of IOP.

Conclusion: Glaucoma

Although glaucoma is one of the most frequently cited medical indications for marijuana, the data do not support this indication. High intraocular pressure (IOP) is a known risk factor for glaucoma and can, indeed, be reduced by cannabinoids and marijuana. However, the effect is too and short lived and requires too high doses, and there are too many side effects to recommend lifelong use in the treatment of glaucoma. The potential harmful effects of chronic marijuana smoking outweigh its modest benefits in the treatment of glaucoma. Clinical studies on the effects of smoked marijuana are unlikely to result in improved treatment for glaucoma.

Future research might reveal a therapeutic effect of isolated cannabinoids. For example, it might be possible to design a cannabinoid drug with longer-lasting effects on IOP and with less psychoactivity than THC.

SUMMARY

Advances in cannabinoid science of the past 16 years have given rise to a wealth of new opportunities for the development of medically useful cannabinoid-based drugs. The accumulated data suggest a variety of indications, particularly for pain relief, antiemesis, and appetite stimulation. For patients such as those with AIDS or who are undergoing chemotherapy, and who suffer simultaneously from severe pain, nausea, and appetite loss, cannabinoid drugs might offer broad-spectrum relief not found in any other single medication. The data are weaker for muscle spasticity but moderately promising. The least promising categories are movement disorders, epilepsy, and glaucoma. Animal data are moderately supportive of a potential for cannabinoids in the treatment of movement disorders and might eventually yield stronger encouragement. The therapeutic effects of cannabinoids are most well established for THC, which is the primary psychoactive ingredient of marijuana. But it does not follow from this that smoking marijuana is good medicine.

Although marijuana smoke delivers THC and other cannabinoids to the body, it also delivers harmful substances, including most of those found in tobacco smoke. In addition, plants contain a variable mixture of

biologically active compounds and cannot be expected to provide a precisely defined drug effect. For those reasons there is little future in smoked marijuana as a medically approved medication. If there is any future in cannabinoid drugs, it lies with agents of more certain, not less certain, composition. While clinical trials are the route to developing approved medications, they are also valuable for other reasons. For example, the personal medical use of smoked marijuana—regardless of whether or not it is approved—to treat certain symptoms is reason enough to advocate clinical trials to assess the degree to which the symptoms or course of diseases are affected. Trials testing the safety and efficacy of marijuana use are an important component to understanding the course of a disease, particularly diseases such as AIDS for which marijuana use is prevalent. The argument against the future of smoked marijuana for treating any condition is not that there is no reason to predict efficacy but that there is risk. That risk could be overcome by the development of a nonsmoked rapid-onset delivery system for cannabinoid drugs.

There are two caveats to following the traditional path of drug development for cannabinoids. The first is timing. Patients who are currently suffering from debilitating conditions unrelieved by legally available drugs, and who might find relief with smoked marijuana, will find little comfort in a promise of a better drug 10 years from now. In terms of good medicine, marijuana should rarely be recommended unless all reasonable options have been eliminated. But then what? It is conceivable that the medical and scientific opinion might find itself in conflict with drug regulations. This presents a policy issue that must weigh—at least temporarily—the needs of individual patients against broader social issues. Our assessment of the scientific data on the medical value of marijuana and its constituent cannabinoids is but one component of attaining that balance.

The second caveat is a practical one. Although most scientists who study cannabinoids would agree that the scientific pathways to cannabinoid drug development are clearly marked, there is no guarantee that the fruits of scientific research will be made available to the public. Cannabinoid-based drugs will become available only if there is either enough incentive for private enterprise to develop and market such drugs or sustained public investment in cannabinoid drug research and development. The perils along this pathway are discussed in chapter 5. Although marijuana is an abused drug, the logical focus of research on the therapeutic value of cannabinoid-based drugs is the treatment of specific symptoms or diseases, not substance abuse. Thus, the most logical research sponsors would be the several institutes within the National Institutes of Health or organizations whose primary expertise lies in the relevant symptoms or diseases.

CONCLUSION: Scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily THC, for pain relief, control of nausea and vomiting, and appetite stimulation; smoked marijuana, however, is a crude THC delivery system that also delivers harmful substances.

RECOMMENDATION: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems.

RECOMMENDATION: Clinical trials of marijuana use for medical purposes should be conducted under the following limited circumstances: trials should involve only short-term marijuana use (less than six months), should be conducted in patients with conditions for which there is reasonable expectation of efficacy, should be approved by institutional review boards, and should collect data about efficacy.

RECOMMENDATION: Short-term use of smoked marijuana (less than six months) for patients with debilitating symptoms (such as intractable pain or vomiting) must meet the following conditions:

- failure of all approved medications to provide relief has been documented,
- the symptoms can reasonably be expected to be relieved by rapid-onset cannabinoid drugs,
- such treatment is administered under medical supervision in a manner that allows for assessment of treatment effectiveness, and
- involves an oversight strategy comparable to an institutional review board process that could provide guidance within 24 hours of a submission by a physician to provide marijuana to a patient for a specified use.

Until a nonsmoked rapid-onset cannabinoid drug delivery system becomes available, we acknowledge that there is no clear alternative for people suffering from *chronic* conditions that might be relieved by smoking marijuana, such as pain or AIDS wasting. One possible approach is to treat patients as *n-of-1* clinical trials, in which patients are fully informed of their status as experimental subjects using a harmful drug delivery system and in which their condition is closely monitored and documented under medical supervision, thereby increasing the knowledge base of the risks and benefits of marijuana use under such conditions. We recom-

mend these *n*-of-1 clinical trials using the same oversight mechanism as that proposed in the above recommendations.

OTHER REPORTS ON MARIJUANA AS MEDICINE

Since 1996, five important reports pertaining to the medical uses of marijuana have been published, each prepared by deliberative groups of medical and scientific experts (Appendix E). They were written to address different facets of the medical marijuana debate, and each offers a somewhat different perspective. With the exception of the report by the Health Council of the Netherlands, each concluded that marijuana can be moderately effective in treating a variety of symptoms. They also agree that current scientific understanding is rudimentary; indeed, the sentiment most often stated is that more research is needed. And these reports record the same problem with herbal medications as noted here: the uncertain composition of plant material makes for an uncertain, and hence often undesirable, medicine.

The 1996 report by the Health Council of the Netherlands concluded that there is insufficient evidence to justify the medical use of marijuana or THC, despite the fact that the latter is an approved medication in the United States and Britain. However, that committee addressed only whether there was sufficient evidence to warrant the prescription of marijuana or cannabinoids, not whether the data are sufficient to justify clinical trials. Conclusions of the Health Council of the Netherlands contrast with that country's tolerance of marijuana use. The health council's report noted that marijuana use by patients in the terminal stages of illness is tolerated in hospitals. It also said that the council did "not wish to judge patients who consume marihuana (in whatever form) because it makes them feel better. . . ."

In contrast, the American Medical Association House of Delegates, National Institutes of Health (NIH), and the British Medical Association recommend clinical trials of smoked marijuana for a variety of symptoms. The NIH report, however, was alone in recommending clinical studies of marijuana for the treatment of glaucoma—and even then there was disagreement among the panel members (William T. Beaver, chair, NIH Ad Hoc Expert Panel on the Medical Use of Marijuana, personal communication, 1998).

Recent reviews that have received extensive attention from those who follow the medical marijuana debate have been written by strong advocates *for* (Grinspoon and Bakalar, 1993⁶²; Zimmer and Morgan, 1997¹⁹⁸) or *against* (Voth and Schwartz, 1997¹⁹¹) the medical use of marijuana. Those reports represent the individual views of their authors, and they are not reviewed here but have been reviewed in major scientific journals.^{7,69,178,180}

REFERENCES

1. Alm A, Camras CB, Watson PG. 1997. Phase III latanoprost studies in Scandanavia, the United Kingdom and the United States. *Survey of Ophthalmology* 41:S105-S110.
2. Alward WL. 1998. Medical management of glaucoma. *The New England Journal of Medicine* 339:1298-1307.
3. AMA (American Medical Association Council on Scientific Affairs). 1997. *Report to the AMA House of Delegates*. Chicago: AMA.
4. Ames FR. 1986. Anticonvulsant effect of cannabidiol. *South African Medical Journal* 69:14.
5. Andreoli TE, Carpenter CC, Bennet CJ, Plum F, eds. 1997. *Cecil Essentials of Medicine*. Fourth Edition. Philadelphia: W.B. Saunders Co.
6. Andrews PL, Davis CJ. 1995. The physiology of emesis induced by anti-cancer therapy. In: Reynolds DJ, Andrews PL, Davis CJ, Editors, *Serotonin and the Scientific Basis of Anti-Emetic Therapy*. Oxford: Oxford Clinical Communications. Pp. 25-49.
7. Bayer R, O'Connell TJ, Lapey JD. 1997. Medicinal uses of marijuana (Letter to the Editor). *Annals of Internal Medicine* 127:1134-1135.
8. Beal JE, Olson RLL, Morales JO, Bellman P, Yangco B, Lefkowitz L, Plasse TF, Shepard KV. 1995. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *Journal of Pain and Symptom Management* 10:89-97.
9. Beal JE, Olson R, Lefkowitz L, Laubenstein L, Bellman P, Yangco B, Morales JO, Murphy R, Powderly W, Plasse TF, Mosdell KW, Shepard KV. 1997. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. *Journal of Pain and Symptom Management* 14:7-14.
10. Bhasin S, Storer TW, Asbel-Sethi N, Kilbourne A, Hays R, Sinha-Hikim I, Shen R, Arver S, Beall G. 1998. Effects of testosterone replacement with a nongenital, transdermal system, Androderm, in human immunodeficiency virus-infected men with low testosterone levels. *Journal Clinical of Endocrinology and Metabolism* 83:3155-3162.
11. Billingsley KG, Alexander HR. 1996. The pathophysiology of cachexia in advanced cancer and AIDS. In: Bruera E, Higginson I, Editors, *Cachexia-Anorexia in Cancer Patients*. New York: Oxford Universtiy Press. Pp. 1-22.
12. Borison HL, McCarthy LE. 1983. Neuropharmacology of chemotherapy-induced emesis. *Drugs* 25:8-17.
13. British Medical Association. 1997. *Therapeutic Uses of Cannabis*. Amsterdam, The Netherlands: Harwood Academic Publishers.
14. Bruera E. 1998. Pharmacological treatment of cachexia: Any progress? *Supportive Care of Cancer* 6:109-113.
15. Calignano A, La Rana G, Giuffrida A, Piomelli D. 1998. Control of pain initiation by endogenous cannabinoids. *Nature* 394:277-281.
16. Camras CB, Alm A, Watson P, Stjernschantz J. 1996. Latanoprost, a prostaglandin analog, for glaucoma therapy: Efficacy and safety after 1 year of treatment in 198 patients. Latanoprost Study Groups. *Ophthalmology* 103:1916-1924.
17. (CDC) Centers for Disease Control. 1992. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR (Morbidity Mortality Weekly Report)* 41(RR-17):1-19.
18. Chang AE, Shiling DJ, Stillman RC, et al. 1979. Delta-9-tetrahydrocannabinol as an antiemetic in patients receiving high-dose methotrexate: A prospective, randomized evaluation. *Annals of Internal Medicine* 91:819-824.
19. Chang AE, Shiling DJ, Stillman RC, Goldberg NH, Seipp CA, Barofsky I, Rosenberg SA. 1981. A prospective evaluation of delta-9-tetrahydrocannabinol as an antiemetic in patients receiving adriamycin and cytoxan chemotherapy. *Cancer* 47:1746-1751.

20. Chauhan BC, Drance SM. 1992. The relationship between intraocular pressure and visual field progression in glaucoma. *Graefe's Archives for Clinical and Experimental Ophthalmology* 230:521–526.
21. Clark RA, Tyson LB, Frisone M. 1985. A correlation of objective and subjective parameters in assessing antiemetic regimens. *Proceedings of the Tenth Anniversary Congress of the Oncology Nursing Society* 2:96.
22. Clark WC, Janal MN, Zeidenberg P, Nahas GG. 1981. Effects of moderate and high doses of marijuana on thermal pain: A sensory decision theory analysis. *Journal of Clinical Pharmacology* 21:299S–310S.
23. Clarke RC. 1995. *Marijuana Botany—An Advanced Study: The Propagation and Breeding of Distinctive Cannabis*. Berkeley, CA: Ronin Publishing.
24. Clifford DB. 1983. Tetrahydrocannabinol for tremor in multiple sclerosis. *Annals of Neurology* 13:669–671.
25. Consroe P. 1998a. Clinical and experimental reports of marijuana and cannabinoids in spastic disorders. In: Nahas GG, Sutin KM, Harvey DJ, Agurell S, Editors, *Marijuana and Medicine*. Totowa, NJ: Humana Press.
26. Consroe P. 1998b. Brain cannabinoid systems as target for the treatment of neurological disorders. *Neurobiology of Disease* 5:534–551.
27. Consroe P, Laguna J, Allender J, Snider S, Stern L, Sandyk R, Kennedy K, Schram K. 1991. Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacology, Biochemistry and Behavior (New York)* 40:701–708.
28. Consroe P, Musty R, Rein J, Tillery W, Pertwee RG. 1997. The perceived effects of smoked cannabis on patients with multiple sclerosis. *European Neurology* 38:44–48.
29. Consroe P, Sandyk R. 1992. Potential role of cannabinoids for therapy of neurological disorders. In: Bartke A, Murphy LL, Editors, *Marijuana/Cannabinoids: Neurobiology and Neurophysiology*. Boca Raton, FL: CRC Press. Pp. 459–524.
30. Consroe P, Sandyk R, Snider SR. 1986. Open label evaluation of cannabidiol in dystonic movement disorders. *International Journal of Neuroscience* 30:277–282.
31. Cooler P, Gregg JM. 1977. Effect of delta-9-tetrahydrocannabinol on intraocular pressure in humans. *Southern Medical Journal* 70:951–954.
32. Crawford WJ, Merritt JC. 1979. Effects of tetrahydrocannabinol on arterial and intraocular hypertension. *International Journal of Clinical Pharmacology and Biopharmacy* 17:191–196.
33. Crow S. 1997. Investigational drugs for eating disorders. *Expert Opinion on Investigational Drugs* 6:427–436.
34. Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel C, Gagliardi R, Sanvito WL, Lander N, Mechoulam R. 1980. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology* 21:175–185.
35. Davis CJ. 1995. Emesis research: A concise history of the critical concepts and experiments. In: Reynolds DJ, Andrews PL, Davis CJ, Editors, *Serotonin and the Scientific Basis of Anti-Emetic Therapy*. Oxford : Oxford Clinical Communications. Pp. 9–24.
36. DeLong MR, Georgopoulos AP, Crutcher MD, Mitchell SJ, Richardson RT, Alexander GE. 1984. Functional organization of the basal ganglia: Contributions of single-cell recording studies. *CIBA Foundation Symposium* 107:64–82.
37. DeMulder PH, Seynaeve C, Vermorker JB, et al. 1990. Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting: A multicenter, randomized, double-blind, crossover study. *Annals of Internal Medicine* 113:834–840.
38. Doblin R, Kleiman MA. 1995. The medical use of marijuana: The case for clinical trials [editorial; comment]. *Journal of Addictive Diseases* 14:5–14; Comment in *Journal of Addictive Diseases* 1994, 13(1):53–65.

39. Doblin R, Kleiman M. 1991. Marijuana as antiemetic medicine: A survey of oncologists' experiences and attitudes. *Journal of Clinical Oncology* 9:1314–1319.
40. Dunlop R. 1996. Clinical epidemiology of cancer cachexia. In: Bruera E, Higginson I, Editors, *Cachexia-Anorexia in Cancer Patients*. Vol. 5. Oxford: Oxford University Press. Pp. 76–82.
41. Dunn M, Davis R. 1974. The perceived effects of marijuana on spinal cord injured males. *Paraplegia* 12:175.
42. Eidelberg D, Moeller JR, Antonini A, Kazumata K, Dhawan V, Budman C, Feigin A. 1997. The metabolic anatomy of Tourette's syndrome. *Neurology* 48:927–934.
43. El-Mallakh RS. 1987. Marijuana and migraine. *Headache* 27:442–443.
44. Engelson ES, Rabkin JG, Rabkin R, Kotler DP. 1996. Effects of testosterone upon body composition. *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology* 11:510–511.
45. Enoch M, Kaye WH, Rotondo A, Greenberg BD, Murphy DL, Goldman D. 1998. 5-HT2A promoter polymorphism-1438G/A, anorexia nervosa, and obsessive-compulsive disorder. *The Lancet* 351:1785–1786.
46. Follmann P, Paltotas C, Suveges I, Petrovits A. 1996–1997. Nocturnal blood pressure and intraocular pressure measurement in glaucoma patients and healthy controls. *International Ophthalmology* 20:83–87.
47. Foltin RW, Fischman MW, Byrne MF. 1988. Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. *Appetite* 11:1–14.
48. Frankel JP, Hughes A, Lees AJ, Stern GM. 1990. Marijuana for Parkinsonian tremor. *Journal of Neurology, Neurosurgery and Psychiatry* 53:436.
49. French J. 1998. The art of antiepileptic trial design. *Advances in Neurology* 76:113–123.
50. Frytak S, Moertel CG, O'Fallon J, et al. 1979. Delta-9-tetrahydrocannabinol as an antiemetic in patients treated with cancer chemotherapy: A double comparison with prochlorperazine and a placebo. *Annals of Internal Medicine* 91:825–830.
51. Glass M, Dragunow M, Faull RLM. 1997. Cannabinoid receptors in the human brain: A detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. *Neuroscience* 77:299–318.
52. Goadsby PJ, Gundlach AL. 1991. Localization of [3H]-dihydroergotamine binding sites in the cat central nervous system: Relevance to migraine. *Annals of Neurology* 29:91–94.
53. Gonzalez EC, Brownlee HJ. 1998. Movement disorders. In: Taylor RB, Editor, *Family Medicine: Principles and Practice*. 5th Edition. New York: Springer-Verlag. Pp. 565–573.
54. Gorter R. 1991. Management of anorexia-cachexia associated with cancer and HIV infection. *Oncology (Supplement)* 5:13–17.
55. Gralla RJ, Itri LM, Pisko SE, et al. 1981. Antiemetic efficacy of high dose metoclopramide: Randomized trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. *New England Journal of Medicine* 305:905–909.
56. Gralla RJ, Navari RM, Hesketh PJ, et al. 1998. Single-dose oral granisetron has equivalent antiemetic efficacy to intravenous ondansetron for highly emetogenic cisplatin-based chemotherapy. *Journal of Clinical Oncology* 16:1–7.
57. Gralla RJ, Rittenberg CN, Lettow LA, et al. 1995. A unique all-oral, single-dose, combination antiemetic regimen with high efficacy and marked cost saving potential. *Proceedings of the American Society for Clinical Oncology* 14:526.
58. Gralla RJ, Tyson LB, Borden LB, et al. 1984. Antiemetic therapy: A review of recent studies and a report of a random assignment trial comparing metoclopramide with delta-9-tetrahydrocannabinol. *Cancer Treatment Reports* 68:163–172.

59. Grandara DR, Roila F, Warr D, Edelman MJ, Perez EA, Gralla RJ. 1998. Consensus proposal for 5HT₃ antagonists in the prevention of acute emesis related to highly emetogenic chemotherapy: Dose, schedule, and route of administration. *Supportive Care in Cancer* 6:237–243.
60. Green K, Roth M. 1982. Ocular effects of topical administration of delta-9-tetrahydrocannabinol in man. *Archives of Ophthalmology* 100:265–267.
61. Greenberg HS, Werness SA, Pugh JE, Andrus RO, Anderson DJ, Domino EF. 1994. Short-term effects of smoking marijuana on balance in patients with multiple sclerosis and normal volunteers. *Clinical Pharmacology and Therapeutics* 55:324–328.
62. Grinspoon L, Bakalar JB. 1993. *Marijuana: The Forbidden Medicine*. New Haven: Yale University Press.
63. Grinspoon L, Bakalar JB, Zimmer L, Morgan JP. 1997. Marijuana addiction [Letter]. *Science* 277:749; discussion, 750–752.
64. Grinspoon S, Corcoran C, Askari H, Schoenfeld D, Wolf L, Burrows B, Walsh M, Hayden D, Parlman K, Anderson E, Basgoz N, Klibanski A. 1998. Effects of androgen administration in men with the AIDS wasting syndrome. *Annals of Internal Medicine* 129:18–26.
65. Gross H, Egbert MH, Faden VB, Godberg SC, Kaye WH, Caine ED, Hawks R, Zinberg NE. 1983. A double-blind trial of delta-9-THC in primary anorexia nervosa. *Journal of Clinical Psychopharmacology* 3:165–171.
66. Guyatt GH, Keller JL, Jaeschke R, Rosenbloom D, Adachi JD, Newhouse MT. 1990. The N-of-1 randomized controlled trial—clinical usefulness: Our three-year experience. *Annals of Internal Medicine* 112:293–299.
67. Guyatt GH, Sackett D, Taylor DW, Chong J, Roberts R, Pugsley S. 1986. Determining optimal therapy: Randomized trials in individual patients. *New England Journal of Medicine* 314:889–892.
68. Guyton AC. 1986. *Textbook of Medical Physiology*. 7th ed. Philadelphia: WB Saunders Company.
69. Hall W. 1997. An ongoing debate. *Science* 278:75.
70. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. 1999. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology* 141:385–394.
71. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. 1999. Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology* 141:395–404.
72. Hanigan WC, Destree R, Truong XT. 1986. The effect of delta-9-THC on human spasticity. *Clinical Pharmacology and Therapeutics* 39:198.
73. Hardin TC. 1993. Cytokine mediators of malnutrition: Clinical implications. *Nutrition in Clinical Practice* 8:55–59.
74. Hayreh SS, Zimmerman MB, Podhajsky P, Alward W. 1994. Nocturnal arterial hypotension and its role in optic nerve head and ocular ischemic disorders. *American Journal of Ophthalmology* 117:603–624.
75. Hemming M, Yellowlees PM. 1993. Effective treatment of Tourette's syndrome with marijuana. *Journal of Psychopharmacology* 7:389–391.
76. Hepler RS, Frank IM, Petrus R. 1976. Ocular effects of marijuana smoking. In: Braude MC, Szara S, Editors, *The Pharmacology of Marijuana*. New York: Raven Press. Pp. 815–824.
77. Hepler RS, Frank IR. 1971. Marijuana smoking and intraocular pressure. *Journal of the American Medical Association* 217(10):1392.
78. Herkenham M, Lynn AB, de Costa BR, Richfield EK. 1991a. Neuronal localization of cannabinoid receptors in the basal ganglia of the rat. *Brain Research* 547:267–274.

79. Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa BR, Rice KC. 1991b. Characterization and localization of cannabinoid receptors in rat brain: A quantitative *in vitro* autoradiographic study. *Journal of Neuroscience* 11:563–583.
80. Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa BR, Rice KC. 1990. Cannabinoid receptor localization in the brain. *Proceedings of the National Academy of Sciences of the United States of America* 87:1932–1936.
81. Herrstedt J, Aapro MS, Smyth JF, Del Favero A. 1998. Corticosteroids, dopamine antagonists and other drugs. *Supportive Care in Cancer* 6:204–214.
82. Hesketh PJ, Gralla RJ, duBois A, Tonato M. 1998. Methodology of antiemetic trials: Response assessment, evaluation of new agents and definition of chemotherapy emetogenicity. *Supportive Care in Cancer* 6:221–227.
83. Hesketh PJ, Kris MG, Grunberg SM, Beck T, Hainsworth JD, Harker G, Aapro MS, Gandara D, Lindley CM. 1997. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *Journal of Clinical Oncology* 15:103–109.
84. Hill SY, Schwin R, Goodwin DW, Powell BJ. 1974. Marijuana and pain. *Journal of Pharmacology and Experimental Therapeutics* 188:415–418.
85. Holdcroft A, Smith M, Jacklin A, Hodgson H, Smith B, Newton M, Evans F. 1997. Pain relief with oral cannabinoids in familial Mediterranean fever. *Anaesthesia* 5:483–486.
86. Homesley HD, Gainey JM, Jobson VN, et al. 1982. Double-blind placebo-controlled study of metoclopramide in cisplatin-induced emesis. *New England Journal of Medicine* 307:250–251.
87. Huestis MA, Henningfield JE, Cone EJ. 1992. Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. *Journal of Analytical Toxicology* 16:276–282.
88. Italian Group for Antiemetic Trials. 1995. Dexamethasone, granisetron, or both for the prevention of nausea and vomiting during chemotherapy for cancer. *New England Journal of Medicine* 332:332–337.
89. Jain AK, Ryan JR, McMahon FG, Smith G. 1981. Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. *Journal of Clinical Pharmacology* 21:320S–326S.
90. Jay WM, Green K. 1983. Multiple-drop study of topically applied 1% Δ^9 -tetrahydrocannabinol in human eyes. *Archives of Ophthalmology* 101:591–593.
91. Jones RT, Benowitz NL, Herning RI. 1981. Clinical relevance of cannabis tolerance and dependence. *Journal of Clinical Pharmacology* 21:143S–152S.
92. Kass MA, Gordon MO, Hoff MR, Pardinson JM, Kolker AE, Hart WM, Becker B. 1989. Topical timolol administration reduces the incidence of glaucomatous damage in ocular hypertensive individuals: A randomized, double-masked, long-term clinical trial. *Archives of Ophthalmology* 107:1590–1598.
93. Kaufman P, Mittag TW. 1994. Medical therapy of glaucoma. In: Kaufman P, Mittag TW, Editors, *Textbook of Ophthalmology*. Volume 7. London: Mosby-Yearbook.
94. Kotler DP. 1997. Wasting Syndrome Pathogenesis and Clinical Markers. *Institute of Medicine Workshop*. Irvine, CA, December 15, 1997. Pp. 56–66. Washington, DC: Institute of Medicine.
95. Kotler DP, Gaetz HP, Klein EB, Lange M, Holt PR. 1984. Enteropathy associated with the acquired immunodeficiency syndrome. *Annals of Internal Medicine* 101:421–428.
96. Kotler DP, Tierney AR, Culpepper-Morgan JA, Wang J, Peirson RN. 1990. Effect of home total parental nutrition on body composition in patients with acquired immunodeficiency syndrome. *Journal of Parenteral Nutrition* 14:454–458.

97. Kotler DP, Tierney AR, Dilmanian FA, Kamen Y, Wang J, Pierson Jr RN, Weber D. 1991. Correlation between total body potassium and total body nitrogen in patients with acquired immunodeficiency syndrome. *Clinical Research* 39:649A.
98. Kotler DP, Tierney AR, Ferraro R, et al. 1991. Enteral alimentation and repletion of body cell mass in malnourished patients with acquired immunodeficiency syndrome. *American Journal of Clinical Nutrition* 53:149–154.
99. Kotler DP, Tierney AR, Wang J, Pierson RN. 1989. Magnitude of body-cell-mass depletion and the timing of death from wasting in AIDS. *American Journal of Clinical Nutrition* 50:444–447.
100. Kotler DP, Wang J, Pierson RN. 1985. Studies of body composition in patients with the acquired immunodeficiency syndrome. *American Journal of Clinical Nutrition* 42:1255–1265.
101. Kris MG, Gralla RJ, Clark RA, et al. 1987. Antiemetic control and prevention of side effects of anticancer therapy with lorazepam or diphenhydramine when used in combination with metoclopramide plus dexamethasone: A double-blind randomized trial. *Cancer* 60:2816–2822.
102. Kris MG, Radford JE, Pizzo BA, et al. 1997. Use of an NK-1 receptor antagonist to prevent delayed emesis following cisplatin. *Journal of the National Cancer Institute* 89:817–818.
103. Kris MG, Roila F, De Mulder PH, Marty M. 1998. Delayed emesis following anticancer chemotherapy. *Supportive Care in Cancer* 6:228–232.
104. Lang IM, Sarna SK. 1989. Motor and myoelectric activity associated with vomiting, regurgitation, and nausea. In: Wood JD, Editor, *Handbook of Physiology: The Gastrointestinal System*. 1, Motility and Circulation. Bethesda, MD: American Physiological Society. Pp. 1179–1198.
105. Larson EB, Ellsworth AJ, Oas J. 1993. Randomized clinical trials in single patients during a 2-year period. *Journal of the American Medical Association* 270:2708–2712.
106. Leske MC, Connell AM, Schachat AP, Hyman L. 1994. The Barbados Eye Study: Prevalence of open angle glaucoma. *Archives of Ophthalmology* 112:821–829.
107. Levitt M, Faiman C, Hawks R, et al. 1984. Randomized double-blind comparison of delta-9-THC and marijuana as chemotherapy antiemetics. *Proceedings of the American Society for Clinical Oncology* 3:91.
108. Libman E, Stern MH. 1985. The effects of delta-9-tetrahydrocannabinol on cutaneous sensitivity and its relation to personality. *Personality, Individuality and Difference* 6:169–174.
109. Lichten PR. 1988. A wolf in sheep's clothing. *Ophthalmology* 95:149–150.
110. Lichtman AH, Cook SA, Martin BR. 1996. Investigation of brain sites mediating cannabinoid-induced antinociception in rats: Evidence supporting periaqueductal gray involvement. *Journal of Pharmacology and Experimental Therapeutics* 276:585–593.
111. Lichtman AH, Martin BR. 1991. Cannabinoid-induced antinociception is mediated by a spinal alpha-noradrenergic mechanism. *Brain Research* 559:309–314.
112. Lindgren JE, Ohlsson A, Agurell S, Hollister LE, Gillespie H. 1981. Clinical effects and plasma levels of delta 9-tetrahydrocannabinol (delta 9-THC) in heavy and light users of cannabis. *Psychopharmacology (Berlin)* 74:208–212.
113. Macallan DC, Noble C, Baldwin C, Foskett M, McManus T, Griffin GE. 1993. Prospective analysis of patterns of weight change in stage IV human immunodeficiency virus infection. *American Journal of Clinical Nutrition* 58:417–424.
114. Malec J, Harvey RF, Cayner JJ. 1982. Cannabis effect on spasticity in spinal cord injury. *Archives of Physical Medicine and Rehabilitation* 63:116–118.

115. Mao LK, Stewart WC, Shields M. 1991. Correlation between intraocular pressure control and progressive glaucomatous damage in primary open-angle glaucoma. *American Journal of Ophthalmology* 111:51–55.
116. Marotta JT. 1995. Spinal injury. In: Rowland LP, Editor, *Merrit's Textbook of Neurology*. 9th Edition. Philadelphia: Lea and Febiger. Pp. 440–447.
117. Martyn CN, Illis LS, Thom J. 1995. Nabilone in the treatment of multiple sclerosis [Letter]. *Lancet* 345:579.
118. Mathew NT. 1997. Serotonin 1D (5-HT 1D) agonists and other agents in acute migraine. *Neurologic Clinics* 15:61–83.
119. Mattes RD, Engelman K, Shaw LM, Elsohly MA. 1994. Cannabinoids and appetite stimulation. *Pharmacology, Biochemistry and Behavior* 49:187–195.
120. Maurer M, Henn V, Dittrich A, Hoffman A. 1990. Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. *European Archives of Psychiatry and Clinical Neuroscience* 240:1–4.
121. McCarthy LE, Flora KP, Vishnuvajjala BR. 1984. Antiemetic properties and plasma concentrations of delta-9-tetrahydrocannabinol against cisplatin vomiting in cats. In: Agurell S, Dewey WL, Willette RE, Editors, *The Cannabinoids: Chemical, Pharmacologic and Therapeutic Aspects*. Orlando, FL: Academic Press. Pp. 859–870.
122. McQuay H, Carroll D, Moore A. 1996. Variation in the placebo effect in randomised controlled trials of analgesics: All is as blind as it seems. *Pain* 64:331–335.
123. Meinck HM, Schonle PW, Conrad B. 1989. Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. *Journal of Neurology* 236:120–122.
124. Merritt JC, Cook CE, Davis KH. 1982. Orthostatic hypotension after delta 9-tetrahydrocannabinol marihuana inhalation. *Ophthalmic Research* 14:124–128.
125. Merritt JC, Crawford WJ, Alexander PC, Anduze AL, Gelbart SS. 1980. Effect of marijuana on intraocular and blood pressure in glaucoma. *Ophthalmology* 87:222–228.
126. Mertens TE, Low-Beer D. 1996. HIV and AIDS: Where is the epidemic going? *Bulletin of the World Health Organization* 74:121–129.
127. Miller AD. 1998. Nausea and vomiting: Underlying mechanisms and upcoming treatments. *Journal of the Japanese Broncho-Esophagological Society* 49:57–64.
128. Miller AD, Nonaka S, Siniatia MS, Jakus J. 1995. Multifunctional ventral respiratory group: Bulospinal expiratory neurons play a role in pudendal discharge during vomiting. *Journal of the Autonomic Nervous System* 54:253–260.
129. Miller AS, Walker JM. 1995. Effects of a cannabinoid on spontaneous and evoked neuronal activity in the substantia nigra pars reticulata. *European Journal of Pharmacology* 279:179–185.
130. Miller AS, Walker JM. 1996. Electrophysiological effects of a cannabinoid on neural activity in the globus pallidus. *European Journal of Pharmacology* 304:29–35.
131. Moertel CG, Taylor WF, Roth A, Tyce FA. 1976. Who responds to sugar pills? *Mayo Clinic Proceedings* 51:96–100.
132. Moldawer LL, Andersson C, Gelin J, Lundholm KG. 1988. Regulation of food intake and hepatic protein synthesis by recombinant-derived cytokines. *American Journal of Physiology* 254:G450–G456.
133. Mulligan K, Tai VW, Schambelan M. 1997. Cross-sectional and longitudinal evaluation of body composition in men with HIV infection. *Journal of Acquired Immunodeficiency Syndrome* 15:43–48.
134. Murray CJL, Lopez AD. 1996. *Global Health Statistics: A Compendium of Incidence, Prevalence, and Mortality Estimates for Over 200 Conditions*. Global Burden of Disease and Injury Series, Volume II. Boston, MA: The Harvard School of Public Health.

135. Navari RM, Reinhardt RR, Gralla RJ, Kris MG, Hesketh PJ, et al. 1999. Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. *The New England Journal of Medicine* 340:190–195.
136. Newell FW, Stark P, Jay WM, Schanzlin DJ. 1979. Nabilone: A pressure-reducing synthetic benzopyran in open-angle glaucoma. *Ophthalmology* 86:156–160.
137. Ng SKC, Brust JCM, Hauser WA, Susser M. 1990. Illicit drug use and the risk of new-onset seizures. *American Journal of Epidemiology* 132:47–57.
138. NIH. 1997. Spinal cord injury: Emerging concepts: An NIH workshop. *Proceedings of an NIH Workshop on Spinal Cord Injury*. Bethesda, MD, September 30–October 1, 1996. Bethesda, MD: National Institute of Neurological Disorders and Stroke.
139. Noyes R, Jr, Brunk SF, Avery DH, Canter A. 1975b. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clinical Pharmacology and Therapeutics* 18:84–89.
140. Noyes Jr R, Brunk SF, Baram DA, Canter A. 1975a. Analgesic effect of delta-9-tetrahydrocannabinol. *Journal of Clinical Pharmacology* 15:139–143.
141. Ohlsson A, Lindgren J-E, Wahlen A, Agurell S, Hollister LE, Gillespie HK. 1980. Plasma delta-9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clinical Pharmacology and Therapeutics* 28:409–416.
142. Orgul S, Kaiser HJ, Flammer J, Gasser P. 1995. Systemic blood pressure and capillary blood-cell velocity in glaucoma patients: A preliminary study. *European Journal of Ophthalmology* 5:88–91.
143. Orr LE, McKernan JF, Bloome B. 1980. Antiemetic effect of tetrahydrocannabinol. Compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. *Archives of Internal Medicine* 140:1431–1433.
144. Ott M, Lambke B, Fischer H, Jagre R, Polat H, Geier H, Rech M, Staszewski S, Helm EB, Caspary WF. 1993. Early changes of body composition in human immunodeficiency virus-infected patients: Tetrapolar body impedance analysis indicates significant malnutrition. *American Journal of Clinical Nutrition* 57:15–19.
145. Perez EA, Chawla SP, Kaywin PK, et al. 1997. Efficacy and safety of oral granisetron versus IV ondansetron in prevention of moderately emetogenic chemotherapy-induced nausea and vomiting. *Proceedings of the American Society for Clinical Oncology* 16:43.
146. Perez-Reyes M, Wagner D, Wall ME, Davis KH. 1976. Intravenous administration of cannabinoids and intraocular pressure. In: *The Pharmacology of Marijuana*, New York: Raven Press. Pp. 829–832.
147. Peroutka SJ. 1996. Drugs effective in the therapy of migraine. In: Hardman JG, Limbird LE, Editors, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 9th Edition. New York: McGraw-Hill. Pp. 487–502.
148. Petro D, Ellenberger Jr C. 1981. Treatment of human spasticity with delta 9-tetrahydrocannabinol. *Journal of Clinical Pharmacology* 21:413S–416S.
149. Quigley HA. 1996. Number of people with glaucoma worldwide. *British Journal of Ophthalmology* 80:389–393.
150. Raft D, Gregg J, Ghia J, Harris L. 1977. Effects of intravenous tetrahydrocannabinol on experimental and surgical pain: Psychological correlates of the analgesic response. *Clinical Pharmacology and Therapeutics* 21:26–33.
151. Razdan RK. 1986. Structure-activity relationships in cannabinoids. *Pharmacology Review* 38:75–149.
152. Richfield EK, Herkenham M. 1994. Selective vulnerability in Huntington's disease: Preferential loss of cannabinoid receptors in lateral globus pallidus. *Annals of Neurology* 36:577–584.

153. Richter A, Loscher W. 1994. (+)-WIN55,212-2 A novel cannabinoid receptor agonist, exerts antidystonic effects in mutant dystonic hamsters. *European Journal of Pharmacology* 264:371–377.
154. Rodriguez de Fonseca F, Carrera MRA, Navarro M, Koob G, Weiss F. 1997. Activation of corticotropin-releasing factor in the limbic system during cannabinoid withdrawal [see comments *Science* 1997., 276:1967–1968]. *Science* 276:2050–2054.
155. Roila F, Tonato M, Cognetti F, et al. 1991. Prevention of cisplatin-induced emesis: A double-blind multicenter randomized crossover study comparing ondansetron and ondansetron plus dexamethasone. *Journal of Clinical Oncology* 9:674–678.
156. Rosenzweig MR, Leiman AL, Breedlove SM. 1996. *Biological Psychology*. Sunderland, MA: Sinauer Associates, Inc.
157. Roth RI, Owen RL, Keren DF, Volberding PA. 1985. Intestinal infection with *Mycobacterium avium* in acquired immune deficiency syndrome (AIDS): Histological and clinical comparison with Whipple's disease. *Digestive Disease Science* 30:497–504.
158. Süttmann U, Ockenga J, Selberg O, Hoogestraat L, Deicher H, Müller MJ. 1995. Incidence and prognostic value of malnutrition and wasting in human immunodeficiency virus—infected outpatients. *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology* 8:239–246.
159. Sackett D, Rosenberg W, Haynes B, Richardson S. 1997. *Evidence-Based Medicine: How to Practice and Teach EBM*. New York: Churchill Livingstone.
160. Sallan SE, Cronin CM, Zelen M, et al. 1980. Antiemetics in patients receiving chemotherapy for cancer: A randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. *New England Journal of Medicine* 302:135–138.
161. Sallan SE, Zinberg NE, Frei E. 1975. Antiemetic effect of delta-9-THC in patients receiving cancer chemotherapy. *New England Journal of Medicine* 293:795–797.
162. SAMHSA (Substance Abuse and Mental Health Services Administration). 1998. *National Household Survey on Drug Abuse: Population Estimates 1997*. DHHS Pub. No. (SMA) 98-3250. Rockville, MD: SAMHSA, Office of Applied Studies.
163. Sandyk R, Awerbuch G. 1988. Marijuana and Tourette's syndrome. *Journal of Clinical Psychopharmacology* 8:444–445.
164. Sandyk R, Consroe P, Stern P, Biklen D. 1988. Preliminary trial of cannabidiol in Huntington's disease. Chesher G, Consroe P, Musty R., Editors, *Marijuana: An International Research Report*. Canberra: Australian Government Publishing Service.
165. Sanudo-Pena MC, Patrick SL, Patrick RL, Walker JM. 1996. Effects of intranigral cannabinoids on rotational behavior in rats: Interactions with the dopaminergic system. *Neuroscience Letters* 206:21–24.
166. Sanudo-Pena MC, Tsou K, and Walker JM. Cannabinoid dopamine interactions in the basal ganglia in an animal model of Parkinson disease. (in preparation).
167. Sanudo-Pena MC, Tsou K, and Walker JM. Superior colliculus and turning: Dopamine and cannabinoids. (in preparation).
168. Sanudo-Pena MC, Walker JM. 1997. Role of the subthalamic nucleus in cannabinoid actions in the substantia nigra of the rat. *Journal of Neurophysiology* 77:1635–1638.
169. Sanudo-Pena MC, Walker JM. 1998. Effects of intrastratial cannabinoids on rotational behavior in rats: Interactions with the dopaminergic system. *Synapse* 30:221–226.
170. Schambelan M, Mulligan K, Grunfeld C, Daar ES, LaMarca A, Kotler DP. 1996. Recombinant human growth hormone in patients with HIV-associated wasting: A randomized, placebo-controlled trial: Serostim Study Group. *Annals of Internal Medicine* 125:873–882.
171. Schwartz RH, Beveridge RA. 1994. Marijuana as an antiemetic drug: How useful is it today? Opinions from clinical oncologists [see Comments]. *Journal of Addictive Diseases* 13:53–65.

172. Schwartz RH, Voth EA. 1995. Marijuana as medicine: Making a silk purse out of a sow's ear. *Journal of Addictive Diseases* 14:15–21.
173. Shields MB. 1998. *Textbook of Glaucoma*. 4th Edition. Baltimore, MD: Williams & Wilkins.
174. Sommer A, Tielsch JM, Katz J, Quigley HA, Gottsch JD, Javitt J, Singh K. 1991. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans: The Baltimore Eye Survey. *Archives of Ophthalmology* 109:1090–1095.
175. Staquet M, Gantt C, Machin D. 1978. Effect of a nitrogen analog of tetrahydrocannabinol on cancer pain. *Clinical Pharmacology and Therapeutics* 23:397–401.
176. Steele N, Gralla RJ, Braun Jr DW. 1980. Double-blind comparison of the antiemetic effects of nabilone and prochlorperazine on chemotherapy-induced emesis. *Cancer Treatments Report* 64:219–224.
177. Stimmel B. 1995. Medical marijuana: To prescribe or not to prescribe, that is the question [Editorial]. *Journal of Addictive Diseases* 14:1–3.
178. Strassman RJ. 1998. *Marijuana: The Forbidden Medicine* (book review). *Journal of the American Medical Association* 279:963–964.
179. Struwe M, Kaempfer SH, Geiger CJ, Pavia AT, Plasse TF, Shepard KV, Ries K, Evans TG. 1993. Effect of dronabinol on nutritional status in HIV infection. *Annals of Pharmacotherapy* 27:827–831.
180. Swift RM. 1994. *Marijuana: The Forbidden Medicine* (book review). *The New England Journal of Medicine* 331:749–750.
181. Tanda G, Pontieri FE, Di Chiara G. 1997. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common μ 1 opioid receptor mechanism. *Science* 276:2048–2049.
182. Tiedeman JS, Shields MB, Weber PA, Crow JW, Cocchetto DM, Harris WA, Howes JF. 1981. Effect of synthetic cannabinoids on elevated intraocular pressure. *Ophthalmology* 88:270–277.
183. Timpone JG, Wright DJ, Li N, Egorin MJ, Enama ME, Mayers J, Galetto G, DATRI 004 Study Group. 1997. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome: The DATRI 004 study group. *AIDS Research and Human Retroviruses* 13:305–315.
184. Trembly B, Sherman M. 1990. Double-blind clinical study of cannabidiol as a secondary anticonvulsant. Unpublished manuscript presented at the Marijuana '90 International Conference on Cannabis and Cannabinoids. Kolympari, Crete, July 8–11.
185. Tyson LB, Gralla RJ, Clark RA, et al. 1985. Phase I trial of levonantradol in chemotherapy-induced emesis. *American Journal of Clinical Oncology* 8:528–532.
186. UNAIDS, WHO. 1998. *Report on the Global HIV/AIDS Epidemic, June 1998*.
187. Ungerleider JT, Andrysiak TA, Fairbanks L, Ellison GW, Myers LW. 1987. Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. *Advances in Alcohol and Substance Abuse* 7:39–50.
188. Vinciguerra V, Moore T, Brennan E. 1988. Inhalation marijuana as an antiemetic for cancer chemotherapy. *New York State Journal of Medicine* 88:525–527.
189. Volicer L, Smith S, Volicer BJ. 1995. Effect of seizures on progression of dementia of the Alzheimer type. *Dementia* 6:258–263.
190. Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. 1997. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry* 12:913–919.
191. Voth EA, Schwartz RH. 1997. Medicinal applications of delta-9-tetrahydrocannabinol and marijuana. *Annals of Internal Medicine* 126:791–798.

192. Wall PD, Melzack R. 1994. *Textbook of Pain*. Edinburgh: Churchill Livingstone.
193. Walters TR. 1996. Development and use of brimonidine in treating acute and chronic elevations of intraocular pressure: A review of safety, efficacy, dose response, and dosing studies. *Survey of Ophthalmology* 41(Suppl. 1):S19-S26.
194. Wang ZM, Visser M, Ma R, Baumgartner RN, Kotler DP, Gallagher D, Heymsfield SB. 1996. Skeletal muscle mass: Validation of neutron activation and dual energy X-ray absorptiometry methods by computerized tomography. *Journal of Applied Physiology* 80:824-831.
195. Whitney EN, Cataldo CB, Rolfes SR. 1994. *Understanding Normal and Clinical Nutrition*. 4th Edition. Minneapolis, MN: West Publishing Co.
196. Wood. 1998. HIV-protease inhibitors. *Drug Therapy* 338:1281-1292.
197. Yoles E, Belkin M, Schwartz M. 1996. HU-211, a nonpsychotropic cannabinoid, produces short- and long-term neuroprotection after optic nerve axotomy. *Journal of Neurotrauma* 13:49-57.
198. Zimmer L, Morgan JP. 1997. *Marijuana Myths, Marijuana Facts*. New York: The Lindesmith Center.

5

Development of Cannabinoid Drugs



Medicines today are expected to be of known composition and quality. Even in cases where marijuana can provide relief of symptoms, the crude plant mixture does not meet this modern expectation. The future of medical marijuana lies in classical pharmacological drug development, and indeed there has been a resurgence of scientific, as well as public, interest in the therapeutic applications of cannabinoids. After an initial burst of scientific activity in the 1970s, today's renewed interest has been fueled by major scientific discoveries discussed in previous chapters: the identification and cloning of endogenous cannabinoid receptors, the discovery of endogenous substances that bind to these receptors, and the emergence of synthetic cannabinoids that also bind to cannabinoid receptors. These scientific accomplishments have propelled interest in developing new drugs that can treat more effectively or more safely the constellation of symptoms for which cannabinoids might have therapeutic benefit (see chapter 4). Through the process of what is referred to as "rational drug design," scientists manipulate the chemical structures of known cannabinoids to design better therapeutic agents. Several new cannabinoids are being developed for human use, but none has reached the stage of human testing in the United States.

The purpose of this chapter is to describe the process of and analyze the prospects for development of cannabinoid drugs. It first discusses the regulatory hurdles that every new drug encounters en route to market. It then proceeds to describe the regulatory and market experiences of

dronabinol (tetrahydrocannabinol, or THC, in sesame oil), the only approved cannabinoid in the United States. These sections serve as a road map to determine whether the therapeutic potential of cannabinoids is likely to be exploited commercially to meet patient needs. Finally, the chapter describes what would be needed to bring marijuana to market as a medicinal plant.

The term *cannabinoids* is used in this chapter to refer to a group of substances that are structurally related to THC—by virtue of a tricyclic chemical structure—or that bind to cannabinoid receptors, such as the natural ligand anandamide. From a chemist's point of view, this definition encompasses a variety of distinct chemical classes. But because the purpose of this chapter is to explore prospects for drug development, both chemical structure and pharmacological activity are important; therefore, the broader definition of cannabinoids is used.

FEDERAL DRUG DEVELOPMENT POLICY

Like controlled substances, cannabinoids developed for medical use encounter a gauntlet of public health regulatory controls administered by two federal agencies: the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (DHHS) and the Drug Enforcement Administration (DEA) of the U.S. Department of Justice. The FDA regulates human testing and the introduction of new drugs into the marketplace, whereas the DEA determines the schedule of and establishes production quotas for drugs with potential for abuse to prevent their diversion to illicit channels. The DEA also authorizes registered physicians to prescribe controlled substances. Some drugs, such as marijuana, are labeled Schedule I in the Controlled Substance Act, and this adds considerable complexity and expense to their clinical evaluation. It is important to point out that Schedule I status does not necessarily apply to all cannabinoids.

Food and Drug Administration

Under the Federal Food, Drug, and Cosmetic (FD&C) Act, the FDA approves new drugs for entry into the marketplace after their safety and efficacy are established through controlled clinical trials conducted by the drugs' sponsors.²³ FDA approval of a drug is the culmination of a long, research intensive process of drug development, which often takes well over a decade.^{19,44} Drug development is performed largely by pharmaceutical companies, but some targeted drug development programs are sponsored by the National Institutes of Health (NIH) to stimulate further development and marketing by the private sector. The NIH's drug devel-

opment programs—including those for AIDS, cancer, addiction, and epilepsy—have been instrumental in ushering new drugs to market in collaboration with pharmaceutical companies.³³ In fact, as noted later, most of the preclinical and clinical research on dronabinol was supported by NIH.

Drug development begins with discovery, that is, the synthesis and purification of a new compound with expected biological activity and therapeutic value. The next major step is the testing of the compound in animals to learn more about its safety and efficacy and to predict its utility for humans. Those early activities are collectively referred to as the pre-clinical phase. When evidence from the preclinical phase suggests a promising role in humans, the manufacturer submits an Investigational New Drug (IND) application to the FDA. The IND submission contains a plan for human clinical trials and includes the results of preclinical testing and other information.²⁰ Absent FDA objection, the IND becomes effective after 30 days, allowing the manufacturer to conduct clinical testing (testing in humans), which generally involves three phases (see Figure 5.1). The three stages of clinical testing are usually the most time-consuming phases of drug development, lasting five years on average.²² The actual time depends on the complexity of the drug, availability of patients, duration of use, difficulty of measuring clinical end points, therapeutic class, and indication (the disease or condition for which the drug has purported benefits).³¹

Drug development is a long and financially risky process. For every drug that ultimately reaches clinical testing through an IND, thousands of drugs are synthesized and tested in the laboratory. And only about one in five drugs initially tested in humans successfully secures FDA approval for marketing through a new drug application (NDA).¹⁹

The manufacturer submits an NDA to the FDA to gain approval for marketing when clinical testing is complete. An NDA is a massive document, the largest portion of which contains the clinical data from Phase I–III testing. The other technical sections of an NDA include chemistry, manufacturing, and controls; nonclinical pharmacology and toxicology; and human pharmacokinetics and bioavailability.²³ In the case of a new cannabinoid, an abuse liability assessment would also probably be part of an NDA submission. In 1996 the median time for FDA review of an NDA, from submission to approval, was 15.1 months, a review period considerably shorter than that in 1990, when the figure was 24.3 months.²² The shortening of approval time is an outgrowth of the Prescription Drug User Fee Act of 1992, which authorized the FDA to hire additional review staff with so-called user fees paid by industry and imposed clear deadlines for FDA action on an NDA. With respect to the cost of a single drug's development, a number of recent studies have provided a range of estimates of

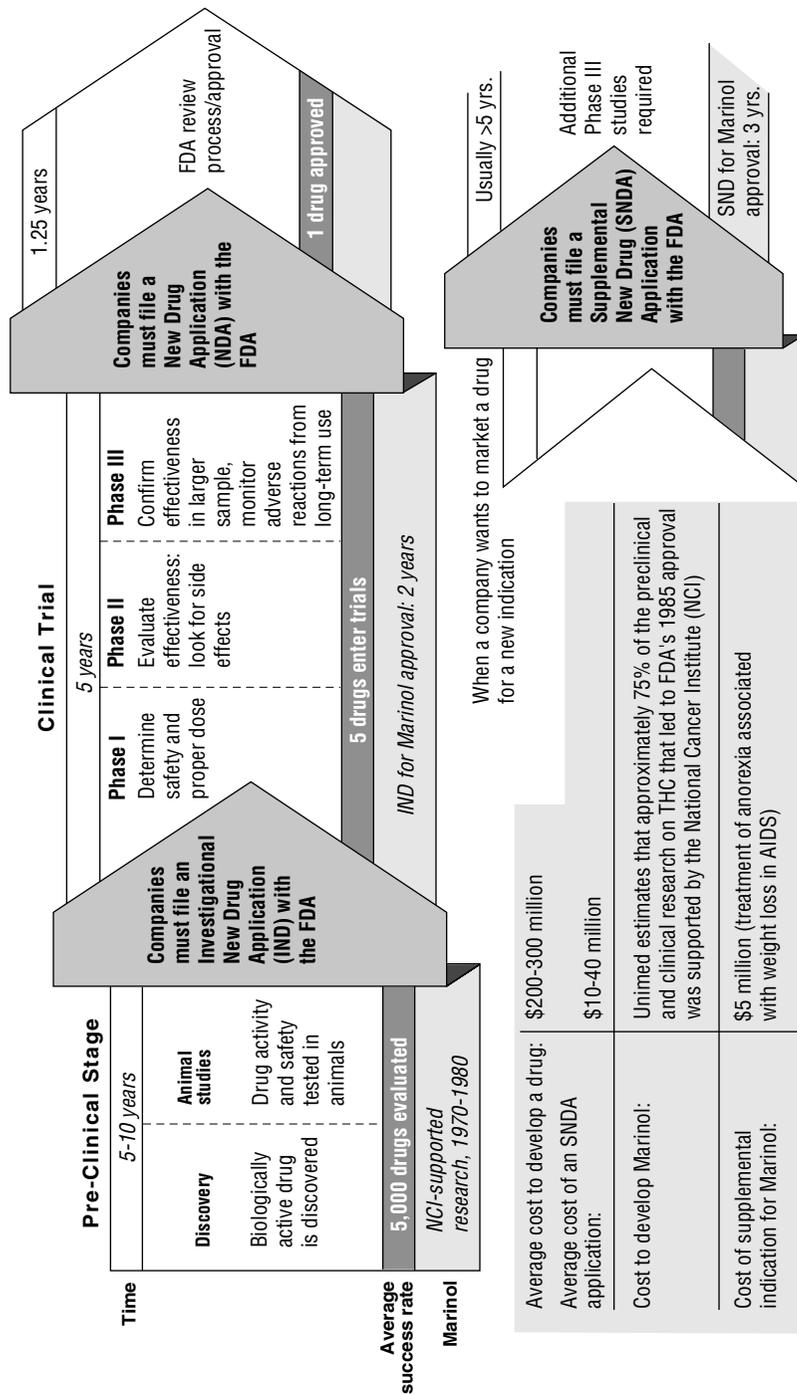


FIGURE 5.1 Stages of clinical testing.

about \$200–\$300 million, depending on the method and year of calculation.^{33,44}

With FDA approval of an NDA, the manufacturer is permitted to market the drug for the *approved indication*. At that point, although any physician is at liberty to prescribe the approved drug for another indication (an “off-label use”), the manufacturer cannot promote it for that indication unless the new indication is granted separate marketing approval by the FDA.* To obtain such approval, the manufacturer is required to compile another application to the FDA for what is known variously as an “efficacy supplement,” a “supplemental application,” or a “supplemental new drug application.” Those terms connote that the application is supplemental to the NDA. In general, collecting new data for FDA approval of an efficacy supplement is not as intensive a process as that for an NDA; it generally requires the firm to conduct two additional Phase III studies, although under some circumstances only one additional study of the drug’s efficacy is needed.²⁴ The preclinical studies, for example, ordinarily need not be replicated. The average cost to the manufacturer for obtaining approval for the new indication is typically about \$10–\$40 million.³³ The review time to obtain FDA approval for the new indication can be considerable; a recent study of supplemental indications approved by the FDA in 1989–1994 found the approval time to exceed that for the original NDA,¹⁸ a reflection, in part, of the lower priority that the FDA accords to the review of efficacy supplements as opposed to new drugs.²³

The manufacturer also must apply to the FDA to receive marketing approval for a new formulation of a previously approved drug. A new formulation is a new dosage form, including a new route of administration. An example of such a new formulation is an inhaled version of Marinol, which is currently approved only in capsule form. The manufacturer is required to establish bioequivalence, safety, and efficacy of the new formulation. The amount of evidence required for approval is highly variable, depending on the similarities between the new formulation and the approved formulation. New formulations are evaluated case by case by the FDA. In the case of Marinol, for example, an inhaled version is likely to require not only new studies of efficacy but also new studies of abuse liability. There appear to be no published peer-reviewed studies of the average cost and time for approval of a new formulation.

Two other FDA programs might be relevant to the potential availabil-

*FDA policies for off-label use are being transformed as a result of the Food and Drug Administration Modernization Act of 1997. The FDA recently promulgated new rules to give manufacturers greater flexibility to disseminate information about off-label uses (FDA, 1998b^{24a}). As of this writing, however, court decisions have left the status of the new rules somewhat unclear.

ity of new cannabinoids. One program is authorized under the Orphan Drug Act of 1983, which provides incentives to manufacturers to develop drugs to treat “orphan diseases.” An orphan disease, as defined in an amendment to the act, is one that affects 200,000 or fewer people in the United States.* The act’s most important incentive is a period of exclusive marketing protection of seven years, during which time the FDA is prohibited from approving the same drug for the same indication.^{5,6} Some of the medical conditions for which cannabinoids have been advocated—Huntington’s disease, multiple sclerosis, and spinal cord injury (see chapter 4)—might meet the definition of an orphan disease and thus enable manufacturers to take advantage of the act’s financial incentives to bring products to market. If a disease affects more than 200,000 people, the manufacturer sometimes subdivides the patient population into smaller units to qualify. For example, a drug for the treatment of Parkinson’s disease is not likely to receive an orphan designation because its prevalence exceeds 200,000, but orphan designation has been accorded to drugs for subsets of Parkinson’s patients, such as those suffering from early-morning motor dysfunction in the late stages of the disease.²⁵

The other program is the Treatment-IND program, which was established by regulation in 1987 (and codified into law in 1997) to allow patients with serious and life-threatening diseases to obtain experimental medications, such as marijuana, before their general marketing.[†] Treatment INDs may be issued during Phase III studies to patients who are not enrolled in clinical trials, provided among other requirements that no comparable alternative drug is available.^{22,32,33} Thus, the treatment IND program can provide a mechanism for some patients to obtain a promising new cannabinoid before its widespread commercial availability if it reached the late stages of clinical testing for a serious or life-threatening disease.

Drug Enforcement Administration

The DEA is responsible for scheduling controlled substances, that is, drugs and other agents that possess a potential for abuse. *Abuse* is generally defined as nonmedical use that leads to health and safety hazards, diversion from legitimate channels, self-administration, and other untoward results.^{15,21} The legislation that gives DEA the authority to regulate

*The FDA can grant orphan designation to a drug intended for a condition that affects a larger population if the manufacturer’s estimated expenses are unlikely to be recovered by sales in the United States (Public Law 98-551).

[†]Marijuana cigarettes were available under a special FDA-sponsored Compassionate Investigational New Drug Program for desperately ill patients until March 1992, when the program was closed to new participants.⁴⁸

drugs of abuse is the Controlled Substances Act, which was passed in 1970 and amended several times. The overall purpose of the CSA is to restrict or control the availability of drugs to prevent their abuse.

Under the CSA, the DEA places each drug that has abuse potential into one of five categories. The five categories, referred to as Schedules I–V, carry different degrees of restriction. Schedule I is the most restrictive, covering drugs that have “no accepted medical use” in the United States and that have high abuse potential. The definitions of the categories and examples of drugs in each are listed in Appendix C. Each schedule is associated with a distinct set of controls that affect manufacturers, investigators, pharmacists, practitioners, patients, and recreational users. The controls include registration with the DEA, labeling and packaging, production quotas, security, recordkeeping, and dispensing.¹⁵ For instance, patients with a legitimate medical need for drugs in Schedule II, the most restrictive schedule for drugs “currently with accepted medical use,” can neither refill their prescriptions nor have them telephoned to a pharmacy (except in an emergency).

The scheduling of substances under the CSA is handled case by case. It may be initiated by DEA, by DHHS, or by petition from an interested party, including the drug’s manufacturer or a public-interest group.¹⁵ The final decision for scheduling rests with the DEA, but for this purpose the secretary of DHHS is mandated to provide a recommendation. The secretary’s recommendation* to DEA is based in part on results from abuse liability testing that the FDA requires of the manufacturer seeking approval of a new drug. Abuse liability testing is not a single test; it is a compilation of several *in vitro* human and animal studies, of which some of the best known are drug self-administration and drug discrimination studies.^{21,34} The secretary’s recommendation for scheduling is formally guided by eight legal criteria, including the drug’s actual or relative potential for abuse, scientific evidence of its pharmacological effect, risk to public health, and its psychic or physiological dependence liability (21 U.S.C. § 811 (b), (c)). Once the DEA receives a scheduling recommendation, its scheduling decision, including the requirement for obtaining public comment, usually takes weeks to months.³³ In practice, the DEA usually adheres to the recommendation of the secretary.[†] Beyond the DEA,

*The FDA and the National Institute of Drug Abuse, two agencies of DHHS, work jointly to develop the medical and scientific analysis that is forwarded to the secretary, who makes a recommendation to the administrator of the DEA (DEA, 1998¹⁵).

†Under the CSA, “the recommendations of the Secretary to the Attorney General shall be binding on the Attorney General as to such scientific and medical matters, and if the Secretary recommends that a drug or other substance not be controlled, the Attorney General shall not control the drug or other substance” (21 U.S.C. § 811 (b)).

various state scheduling laws also affect the manufacture and distribution of controlled substances.^{33,50}

Under the CSA, marijuana and THC* are in Schedule I, the most restrictive schedule. The scheduling of any other cannabinoid under this act first hinges on whether it is found *in the plant*. All cannabinoids in the plant are automatically in Schedule I because they fall under the act's definition of marijuana (21 U.S.C. § 802 (16)). In addition, under DEA's regulations, synthetic equivalents of the substances contained in the plant and "synthetic substances, derivatives, and their isomers" whose "chemical structure and pharmacological activity" are "similar" to THC also are automatically in Schedule I (21 CFR § 1308.11(d)(27). Based on the examples listed in the regulations, the word *similar* probably limits the applicability of the regulation to isomers of THC, but DEA's interpretation of its own regulations would carry significant weight in any specific situation.

Prompted by a 1995 petition from Jon Gettman, a former president of the National Organization for the Reform of Marijuana Laws (NORML), to remove marijuana and THC from Schedule I, DEA gathered information which was then submitted to DHHS for a medical and scientific recommendation and scheduling recommendation, as required by the CSA. For the reasons noted above, any changes in scheduling of marijuana and THC would also affect other plant cannabinoids. For the present, however, any cannabinoid found in the plant is automatically controlled in Schedule I.

Investigators are affected by Schedule I requirements even if their research is being conducted *in vitro* or on animals. For example, researchers studying cannabinoids found in the plant are required under the CSA to submit their research protocol to DEA, which issues a registration that is contingent on FDA's evaluation and approval of the protocol (21 CFR § 1301.18). DEA also inspects the researcher's security arrangements. However, the regulatory implications are quite different for cannabinoids *not found in the plant*. Such cannabinoids appear to be uncontrolled unless the FDA or DEA decides that they are sufficiently similar to THC to be placed automatically into Schedule I under the regulatory definition outlined above or the FDA or the manufacturer deems them to have potential for abuse, thereby triggering *de novo* the scheduling process noted above. Thus far, the cannabinoids most commonly used in preclinical research (Table 5.1) appear to be sufficiently distinct from THC that they are not currently considered controlled substances by definition (F. Sapienza, DEA, personal communication, 1998). No new cannabinoids other than

*Technically, the CSA and the regulations use the term "tetrahydrocannabinols."

TABLE 5.1 Cannabinoids and Related Compounds Commonly Used in Research**Agonists**

THC

WIN 55,212-2

CP-55940

HU-210

Anandamide (natural ligand)

2-Arachidonylglycerol (natural ligand)

Antagonists

SR 141716A

SR 144528

SOURCES: Felder and Glass (1998)²⁶ and Mechoulam et al. (1998).³⁶

THC have yet been clinically tested in the United States, so scheduling experience is limited. The unscheduled status of some cannabinoids might change as research progresses. Results of early clinical research could lead a manufacturer to proceed with or lead the FDA to require abuse liability testing. Depending on the results of such studies, DHHS might or might not recommend scheduling *de novo* to DEA, which makes the final decision case by case.

Will newly discovered cannabinoids be subject to scheduling? That is a complex question that has no simple answer. The answer depends entirely on each new cannabinoid—whether it is found in the plant, its chemical and pharmacological relationship to THC, and its potential for abuse. Novel cannabinoids with strong similarity to THC are likely to be scheduled at some point before marketing, whereas those with weak similarity might not be. The manufacturer's submission to FDA, which contains its own studies and its request for a particular schedule, can also shape the outcome. Cannabinoids found in the plant are automatically in Schedule I until the manufacturer requests and provides justification for rescheduling. The CSA does permit DEA to reschedule a substance (move it to a different schedule) and to deschedule a substance (remove it from control under the CSA) according to the scheduling criteria (see Appendix F) and the process outlined above.

The possibility of scheduling is a major determinant of whether a manufacturer proceeds with drug development.³³ In general, pharmaceutical firms perceive scheduling to be a deterrent because it limits their ability to achieve market share for the following reasons: restricted access,

physician disinclination to prescribe scheduled substances, stigma, the additional expense for abuse liability studies, and expensive delays in reaching the market due to federal and state scheduling processes.³³ Empirical evidence to support that widely held perception is difficult to find, but at least one large survey of physicians found them to have moderate concerns about prescribing opioids because of actual or perceived pressure from regulatory agencies, such as DEA.⁵⁷ On the basis of a legal analysis and widespread complaints from researchers and pharmaceutical executives, the Institute of Medicine (IOM, 1995)³³ recommended changes in the CSA to eliminate the act's barriers to undertaking clinical research and development of controlled substances; this position was supported in a later report on marijuana.⁴⁰

DEVELOPMENT AND MARKETING OF MARINOL

The following material is based on the published literature (where cited), workshops sponsored by the IOM, and an interview with Robert Dudley, senior vice president of Unimed Pharmaceuticals, Inc., the manufacturer of Marinol and the holder of the NDA. Unimed markets Marinol jointly with Roxane Laboratories, Inc.

Marinol (dronabinol) is the only cannabinoid with approval for marketing in the United States.* The following description covers its development, regulatory history, pharmacokinetics, adverse effects, abuse liability, and market growth. The experience with Marinol can serve as a possible bellwether for the regulatory and commercial fate of new cannabinoids being considered for development.

Development and Regulatory History

Marinol is manufactured as a capsule containing THC in sesame oil; it is taken orally. It was approved by the FDA in 1985 for the treatment of nausea and vomiting associated with cancer chemotherapy. In 1992, the FDA approved marketing of dronabinol for the treatment of anorexia associated with weight loss in patients with AIDS.⁴⁵ The preclinical and clinical research on THC that culminated in the FDA's 1985 approval was supported primarily by the National Cancer Institute (NCI), whose research support goes back to the 1970s. NCI's contribution appears pivotal, considering that Unimed, the pharmaceutical company that holds

*The only cannabinoid licensed outside the United States is nabilone (Cesamet), which is an analogue of THC available in the United Kingdom for the management of nausea and vomiting associated with cancer chemotherapy (Pertwee, 1997).⁴⁶

the NDA, estimates its contribution to have been only about 25% of the total research effort. The FDA's review and approval of Marinol took about two years after submission of the NDA, according to Unimed. To obtain approval for Marinol's second indication (through an efficacy supplement), the FDA required two more relatively small Phase III studies. The studies lasted three years and cost \$5 million to complete.

Physical Properties, Pharmacokinetics, and Adverse Events

Marinol is synthesized in the laboratory rather than extracted from the plant. Its manufacture is complex and expensive because of the numerous steps needed for purification. The poor solubility of Marinol in aqueous solutions and its high first-pass metabolism in the liver account for its poor bioavailability; only 10–20% of an oral dose reaches the systemic circulation.^{45,60} The onset of action is slow; peak plasma concentrations are not attained until two to four hours after dosing.^{45,56} In contrast, inhaled marijuana is rapidly absorbed. In a study comparing THC administered orally, by inhalation, and intravenously, plasma concentration peaked almost instantaneously after both inhalation and intravenous administration; most participants' peak plasma concentrations after oral administration occurred at 60 or 90 minutes. Variation in individual responses is highest for oral THC and bioavailability is lowest.⁴²

Marinol's most common adverse events are associated with the central nervous system (CNS): anxiety, confusion, depersonalization, dizziness, euphoria, dysphoria, somnolence, and thinking abnormality.^{8,9,45,59} In two recent clinical trials, CNS adverse events occurred in about one-third of patients, but only a small percentage discontinued the drug because of adverse effects.^{8,9} Lowering the dose of dronabinol can minimize side effects, especially dysphoria (disquiet or malaise).⁴⁷

Abuse Potential and Scheduling

On commercial introduction in 1985, Marinol was placed in Schedule II. This schedule, the second most restrictive, is reserved for medically approved substances that have "high potential for abuse" (21 U.S.C. § 812 (b) (2)). Unimed did not encounter any delays in marketing as a result of the scheduling process because the scheduling decision was made by the DEA before FDA's approval for marketing. Nor did Unimed encounter any marketing delays as a result of state scheduling laws. Unimed was not specifically asked by the FDA to perform abuse liability studies for the first approval, presumably because such studies had been conducted earlier.

Unimed later petitioned the DEA to reschedule Marinol from Sched-

ule II to Schedule III, which is reserved for medically approved substances that have some potential for abuse (21 U.S.C. § 812 (b) (3)). To buttress its request for rescheduling, Unimed supported an analysis of Marinol's abuse liability by researchers at the Haight Ashbury Free Clinic of San Francisco, which treats many cannabis-dependent patients and people who have HIV/AIDS. The analysis found no evidence of abuse or diversion of Marinol after a literature review and surveys and interviews of medical specialists in addiction, oncology, cancer research, and treatment of HIV, and people in law enforcement. The authors attribute Marinol's low abuse potential to its slow onset of action, its dysphoric effects, and other factors.¹² On November 5, 1998, the DEA announced a proposal to reschedule Marinol to Schedule III.¹⁷ As of this writing, no formal action on that proposal had been taken.

The rescheduling of a drug from Schedule II to Schedule III is considered important because it lifts some of the restrictions on availability. For example, Unimed expects a sales increase of about 15–20% as a result of rescheduling. In its judgment and that of many other pharmaceutical companies,³³ scheduling limits market penetration; the more restrictive the schedules, the greater the limitation. The reasons are that physicians and other providers are reluctant to prescribe Schedule II drugs; patients are deterred from seeking prescriptions because of Schedule II prohibition of refills, as opposed to other commercially available scheduled substances; additional restrictions are imposed by several states, such as quantity restrictions (for example, 30-day supply limits) and triplicate prescriptions;⁵⁰ and some Schedule II drugs are excluded from hospital formularies because of onerous security and paperwork requirements under federal and state controlled substances laws.

Market Growth and Transformation

Annual sales of Marinol are estimated at \$20 million, according to Unimed. Of Marinol's patient population 80% use it for HIV, 10% for cancer chemotherapy, and about 5–10% for other reasons. The latter group is thought to consist of Alzheimer's patients drawn to the drug by a recently published clinical study indicating Marinol's promise for the treatment of their anorexia and disturbed behavior.⁵⁸ As noted earlier, Unimed cannot promote Marinol for this unlabeled indication, but physicians are free to prescribe it for such an indication. Unimed is conducting additional research in pursuit of FDA approval of a new indication for Marinol in the treatment of Alzheimer disease.

The 1992 approval of Marinol for the treatment of anorexia in AIDS patients marked a major transformation in the composition of the patient population. Marinol's use had been restricted to oncology patients. The

oncology market for Marinol gradually receded as a result of the introduction of newer medications, including such serotonin antagonists as ondansetron, which are more effective (see chapter 4, "Nausea and Vomiting") and are not scheduled. Much of the recent growth of the market for Marinol (which is about 10% per year) is attributed to its increasing use by HIV patients being treated with combination antiretroviral therapy. Marinol appears to have a dual effect, not only stimulating appetite but also combating the nausea and vomiting associated with combination therapy. Unimed is supporting a Phase II study to examine this combined effect and, with promising results, plans to seek FDA approval for this new indication.

Unimed has two forms of market protection for Marinol. In December 1992, the FDA granted Marinol seven years of exclusive marketing under the Orphan Drug Act. The market exclusivity is related to Marinol's use in anorexia associated with AIDS. Because of the designated orphan indication, the active ingredient, THC, cannot be marketed by another manufacturer for the same indication until December 1999. Other pharmaceutical manufacturers are not constrained from manufacturing and marketing THC for its *other* indication, antiemesis for cancer chemotherapy, but none appears to be interested in what is, by pharmaceutical company standards, a small market. In addition to market exclusivity, Unimed secured in June 1998 a "use patent" for dronabinol for the treatment of disturbed patients with dementia; this confers patent protection to Unimed for this use for 20 years from the date of filing of the application,* assuming that this indication eventually gains FDA approval.

The rate-limiting factors in the growth of the market for Marinol, according to Unimed are the lack of physician awareness of the drug's efficacy, its adverse effects, and its restricted availability as a result of placement in Schedule II. Unimed perceives only a small percentage of its market to be lost to "competition" from marijuana itself, but there are, admittedly, no reliable statistics on the number of people who have chosen to treat their symptoms with illegally obtained marijuana, despite their ability to obtain Marinol.

New Routes of Administration

It is well recognized that Marinol's oral route of administration hampers its effectiveness because of slow absorption and patients' desire for

*A use patent—also known as a process patent—accords protection for a method of using a composition or compound. A use patent is not considered as strong as a product patent, which prohibits others from manufacturing, using, or selling the product for all uses, rather than for the specific use defined in a use patent.

more control over dosing. A drug delivered orally is first absorbed from the stomach or small intestine and then passed through the liver, where it undergoes some metabolism before being introduced into the circulation. To overcome the deficiencies of oral administration, Unimed activated an IND in 1998 as a step toward developing new formulations for Marinol. Four new formulations—deep lung aerosol, nasal spray, nasal gel, and sublingual preparation—are under study in Phase I clinical studies being conducted in conjunction with Roxane Laboratories. These formulations seek to deliver Marinol to the circulation more rapidly and directly. The first two fall under inhalation as a route of administration. Inhalation is considered the most promising method, owing to the rapidity of onset of its effects and potential for better titration of the dose by the patient, but it might also carry an increased potential for abuse. The abuse of a drug correlates with its rapidity of onset (G. Koob, IOM workshop). Sublingual route (under the tongue) administration also affords rapid absorption into the circulation, in this case from the oral mucosa. Other researchers are pursuing the delivery of THC through rectal suppositories, but this slower route might not be acceptable to many patients. Transdermal (skin patches) administration, which is best suited to hydrophilic drugs, is precluded by the lipophilicity of THC. Thus, the choice of routes of administration depends heavily on the physicochemical characteristics of the drug and on its safety, abuse liability, and tolerability.

Unimed expects the FDA to require it to conduct studies of the bioavailability, efficacy, and possibly abuse liability of any new formulation it seeks to market. Any formulation that expedites Marinol's onset of action, as suggested above, is thought to carry greater possibility of abuse. The cost of developing each new formulation is estimated by Unimed at \$7–\$10 million.

Unimed and Roxane are developing, or considering development of, five new indications for Marinol: disturbed behavior in Alzheimer's disease, nausea and vomiting in HIV patients who are receiving combination therapy, spasticity in multiple sclerosis, intractable pain, and anorexia in cancer and renal disease.

Costs of Marinol and Marijuana

During the IOM public workshops held during the course of this study, many people commented that an important advantage of using marijuana for medical purposes is that it is much less expensive than Marinol. But this comparison is deceptive. While the direct costs of marijuana are relatively low, the indirect costs can be prohibitive. Individuals who violate federal or state marijuana laws risk a variety of costs associated with engaging in criminal activity, ranging from increased vulner-

ability to theft and personal injury legal fees to long prison terms. In addition, when purchasing illicit drugs there is no guarantee that the product purchased is what the seller claims it is or that it is not contaminated.

The price of Marinol for its most commonly used indication, anorexia in AIDS, is estimated at \$200 per month. The less common indication—nausea and vomiting with cancer chemotherapy—is not as expensive because it is not chronic. Regardless of indication, patients' out-of-pocket expenses tend to be much less—often minimal—because of reimbursement through public or private health insurance. For indigent patients who are uninsured, Roxane sponsors a patient assistance program to defray the cost.

The street value of marijuana, according to the DEA's most recent figures, is about \$5–\$10 per bag of loose plant.^{16*} At the California buyers' clubs, the price is \$2–\$16 per gram, depending on the grade of marijuana. The cost to a patient using marijuana depends on the number of cigarettes smoked each day, their THC content, and the duration of use. Insurance does not cover the cost of marijuana. In addition, it is possible for a person to cultivate marijuana privately with little financial investment.

Thus, Marinol appears to be less expensive than marijuana for patients with health insurance or with financial assistance from Roxane. But if the full cost of Marinol is borne out of pocket by the patient, the cost comparison is not so unambiguous. In this case the daily cost in relation to marijuana varies according to the number of cigarettes smoked: If the patient smokes two or more marijuana cigarettes per day, Marinol might be less expensive than marijuana; if the patient smokes only one marijuana cigarette per day, Marinol might be more expensive than marijuana, according to an analysis submitted to the DEA by Unimed. The cost comparisons will depend on fluctuations in the retail price and street value of Marinol and marijuana, respectively, and will vary if marijuana becomes commercially available.

In summary, Marinol has been on the U.S. market since 1985. Its commercial development depended heavily on research supported by the NIH. Marinol's market has grown to \$20 million in annual sales. Further market growth is expected but is still constrained by lack of awareness, adverse effects, the oral route of administration, and restrictions imposed by drug scheduling. The manufacturer is proceeding with research on new forms of delivery to overcome the problems associated with oral administration. The manufacturer also is proceeding with research on an array of new indications for Marinol.

*The DEA did not provide an estimate of the weight of marijuana per bag.

MARKET OUTLOOK FOR CANNABINOIDS

The potential therapeutic value of cannabinoids is extremely broad. It extends well beyond antiemesis for chemotherapy and appetite stimulation for AIDS, the two indications for which the FDA has approved dronabinol (Marinol). Chapter 4 of this report assesses the possible wider therapeutic potential of marijuana and THC in neurological disorders, glaucoma, and analgesia—all conditions for which clinical research has been under way to fulfill unmet patient needs. New therapeutic uses are being explored in preclinical research. For any of these therapeutic indications, will novel cannabinoids reach the market to satisfy the medical needs of patients?

Economic Factors in Development

The outcomes of preclinical and clinical research determine whether a drug is sufficiently safe and effective to warrant FDA approval for marketing. But the decisions to launch preclinical research and to proceed to clinical trials if early results are promising are dictated largely by economic factors. A pharmaceutical company must decide whether to invest in what is universally regarded as a long and risky research path. For any given drug the question is, Will there be an adequate return on investment? The investment in this case is the high cost of developing a drug. The expectation of high financial returns on investment is what drives drug development.^{44,53}

Market analyses are undertaken to forecast whether a drug will reap a substantial return on investment. The market analysis for a cannabinoid is likely to be shaped by various factors. The average cost of developing a cannabinoid is likely to be higher than that of developing other drugs if its clinical indication is in the therapeutic categories of neuropharmaceutical or nonsteroidal antiinflammatory drug, the two therapeutic categories associated with the highest research and development costs.¹⁹ One reason for higher costs is the need to satisfy the DEA's regulatory requirements related to drug scheduling.

On the "market return" side are multiple factors. A market analysis examines the expected returns from the possible markets for which a cannabinoid could be clinically pursued. The financial size of each market is calculated mostly on the basis of the current and projected patient prevalence (for a given clinical indication), sales data (if available), and competition from other products. The duration of use is also factored in—a drug needed for long-term use in a condition with an early age of onset is desirable from a marketing perspective. Factors that can augment or diminish market return include patentability and other forms of market protection,

TABLE 5.2 Cannabinoids Under Development for Human Use

Name of Drug	Investigator	Stage of Development	Pharmacology	U.S. FDA Status	Possible Indication(s)
HU-211	Pharmos Corp.	Clinical Phase II in Israel	NMDA receptor antagonist	None	Neuroprotection (neurotrauma, stroke, Parkinson's, Alzheimer's)
CT-3	Atlantic Pharmaceuticals	Preclinical	Nonpsychoactive	None	Antiinflammatory analgesia
THC	Unimed Roxane Labs	Clinical Phase I	Cannabinoid receptor agonist	IND	(See text)
Marijuana plant	HortaPharm	Clinical in England ^a	Cannabinoid mixture	None	Multiple sclerosis
	GW Pharmaceuticals	Clinical Phase I	Cannabinoid mixture	IND	HIV-related appetite stimulation
	Donald Abrams, M.D.		Cannabinoid mixture	IND	Migraine
	Ethan Russo, M.D.		Cannabinoid mixture	IND pending	

^aClinical trials are to proceed in the next few years under a license from the British Home Office.¹⁰

SOURCES: Glain, 1998²⁷; Atlantic Pharmaceuticals, 1997⁷; Striem et al., 1997⁵⁵; Nainggolan, 1997³⁷; Zurier et al., 1998⁶¹; D. Abrams and E. Russo, personal communications, 1998; R. Dudley, personal communication, 1998; Pharmaprojects Database, 1998.

reimbursement climate, restrictions in access due to drug scheduling, social attitudes, adverse effect profile, and drug interactions.^{33,53} New cannabinoids generally can receive product patents, giving the patent holder 20 years of protection from others seeking to manufacture or sell the same product. According to U.S. patent law, the product must be novel and "nonobvious" in relation to prior patents.²⁸

Cannabinoids under Development

From publicly available sources, the IOM was able to learn of several cannabinoids being developed for human use (Table 5.2). With the exception of Marinol and marijuana, all are in the preclinical phase of testing in the United States. This list might not be comprehensive, inasmuch as other compounds could be under development, but that information is

proprietary.* The table does not list the full complement of cannabinoids, both agonists and antagonists, being used in research as tools to understand the pharmacology of cannabinoids (for more comprehensive lists of cannabinoids, see Felder and Glass, 1998²⁶; Mechoulam et al., 1998³⁶; Howlett, 1995³⁰; Pertwee 1997⁴⁶). Nor does it list cannabinoids once considered for development but later discontinued. An 18-year survey of analgesics in development in 1980–1998 found that six of the nine cannabinoids under development for analgesia were discontinued or undeveloped,^{49,†} but work on most of these was halted before 1988, when the first endogenous cannabinoid receptor was discovered (chapter 3).

Three points can be made on the basis of Table 5.2. First, virtually all of the listed cannabinoids are being developed by small pharmaceutical companies or by individuals. In general, that implies that their development is considered especially risky from a commercial standpoint in that small companies are often willing to assume greater development risks than larger more established firms (W. Schmidt, personal communication, 1998). Without the benefit of sales revenues, small companies are able to fund their research through financing from venture capital, stock offerings, and relationships with established pharmaceutical companies.⁴³

Second, with the exception of THC, no constituents of the marijuana plant appear to be undergoing development by pharmaceutical companies. A number of plant compounds have been tested in experimental models and humans. For example, the antiemetic properties and negligible side effects of Δ^8 -THC were demonstrated in a clinical trial in children who were undergoing cancer chemotherapy,¹ but no sponsor was interested in developing Δ^8 -THC for commercial purposes (R. Mechoulam, Hebrew University, personal communication, 1998). The absence of plant cannabinoids under development implies that the specter of automatic placement in Schedule I under the CSA is an important deterrent, even though rescheduling would occur before marketing.^{††} The point from the earlier discussion is that automatic, as opposed to *de novo*, scheduling appears to cast a pall over development of a cannabinoid found in the plant. Another impediment is that a cannabinoid extracted

*Information about the existence of an IND is proprietary; it can be confirmed only by the manufacturer, not the FDA.

†Discontinued: levonantradol, nabitan, nantradol, and pravadoline. Undeveloped: CP-47497 and CP-55244.

††As a result of the FDA's approval of an NDA, the drug would be, at a minimum, rescheduled in Schedule II. Depending on abuse liability data supplied by the manufacturer and the FDA's recommendation, the drug could be moved to a less restrictive schedule or be descheduled.

from the plant is not likely to fulfill the criteria for a product patent, although other forms of market protection are possible. Marinol, for example, was accorded orphan drug status and its manufacturer obtained a use patent.

Third, cannabinoids are being developed for therapeutic applications beyond those discussed earlier in this chapter and in chapter 4. One of the most prominent new applications of cannabinoids is for “neuroprotection,” the rescue of neurons from cell death associated with trauma, ischemia, and neurological diseases.^{29,36} Cannabinoids are thought to be neuroprotective—through receptor-dependent⁵¹ as well as receptor-independent pathways; both THC, which binds to CB₁ receptors, and CBD, which does not, are potent antioxidants, effective neuroprotectants because of their ability to reduce the toxic forms of oxygen (free radicals) that are formed during cellular stress.²⁹ The synthetic cannabinoid HU-211 (dexanabinol) is an antioxidant and an antagonist of the NMDA receptor, rather than an agonist at the cannabinoid receptor.⁵² Earlier research demonstrated that HU-211 protects neurons from neurotoxicity induced by excess concentrations of the excitatory neurotransmitter glutamate. Excess release of glutamate, which acts by binding to the NMDA receptor, is associated with trauma and disease.⁵⁴ As an NMDA antagonist, HU-211 blocks the damaging action of glutamate and other endogenous neurotoxic agents.^{52,55} After having been studied in the United Kingdom in Phase I clinical trials, HU-211 progressed to Phase II clinical trials in Israel for treatment of severe closed-head trauma (Knoller et al., 1998).³⁵

Market Prospects

It is difficult to gauge the market prospects for new cannabinoids. There certainly appears to be scientific interest, particularly for the discovery of new cannabinoids, but whether this interest can be sustained commercially through the arduous course of drug development is an open question. Research and development experience is limited; only one cannabinoid, dronabinol, is commercially available, and most of its research and development costs were shouldered by the federal government. Furthermore, the size of dronabinol’s market (at about \$20 million) is modest by pharmaceutical company standards. None of the other cannabinoids in development has reached clinical testing in the United States. Their scientific, regulatory, and commercial fates are likely to be very important in shaping future investment patterns. Experience with the drug scheduling process also is likely to be watched very carefully. If the early products are heavily regulated in the absence of strong abuse liability, future development might be deterred. For the present, what seems to be clear

from the dearth of products in development and the small size of the companies sponsoring them is that cannabinoid development is seen as especially risky.

One scenario is that cannabinoids will be pursued for lucrative markets that reflect large unmet medical needs. Of the therapeutic needs for which cannabinoid receptor agonists have been tested, analgesia is by far the largest. The annual U.S. prescription and over-the-counter analgesic market in 1997 was \$4.4 billion.⁴⁹ Given the long-standing need for less addictive, safer, easier to use, and more effective drugs for acute and chronic pain, it would not be surprising to see cannabinoids developed to treat some segments of the current analgesic market, if their safety and effectiveness were clearly established in clinical trials.

In addition to cannabinoid receptor agonists, two classes of cannabinoid-related drugs might prove therapeutically useful: cannabinoid antagonists and inverse agonists, compounds that bind to receptors but produce effects opposite those of agonists. Neither would be subject to the same scheduling concerns as cannabinoid agonists because they are not found in marijuana and would be highly unlikely to have any abuse potential. Another set of cannabinoid-related drugs, such as those that affect the synthesis, uptake, or inactivation of endogenous cannabinoids might, however, have abuse potential because they would influence the signal strength of endogenous cannabinoids.

The development of specific cannabinoid antagonists, like SR141716A for CB₁ receptors and SR144528 for CB₂ receptors, has provided a substantial impetus to understand cannabinoid actions. Those compounds block many of the effects of THC in animals, and their testing in humans has just begun. Cannabinoid antagonists have physiological effects on their own, in the absence of THC. They might have important therapeutic potential in a variety of clinical situations. For example, THC reduces short-term memory, so it is possible that a CB₁ antagonist like SR141716A could act as a memory-enhancing agent. Similarly, for conditions in which cannabinoids decrease immune function (presumably by binding to CB₂ receptors in immune cells), a CB₂ antagonist might be useful as an immune stimulant.

Cannabinoid inverse agonists would exert effects opposite those of THC and might thus cause appetite loss, short-term memory enhancement, nausea, or anxiety. Those effects could possibly be separated by molecular design, in which case inverse agonists might have some therapeutic value. One report has been published suggesting that the CB₁ receptor antagonist, SR141617A,¹¹ is an inverse agonist, and there will likely be others.

REGULATION OF AND MARKET OUTLOOK FOR MARIJUANA

Marijuana is not legally marketed in the United States.* No sponsor has ever sought marketing approval from the FDA for medical use of marijuana. One sponsor has an IND for a clinical safety study on HIV anorexia (D. Abrams, University of California at San Francisco, personal communication, 1998). Another has an IND pending for the treatment of migraine headaches (E. Russo, Western Montana Clinic, personal communication, 1998). Since 1970, marijuana's manufacture and distribution have been tightly restricted under the CSA, which places marijuana in Schedule I, which is reserved for drugs or other substances with "a high potential for abuse," "no currently accepted medical use," and "lack of accepted safety for use . . . under medical supervision" (21 U.S.C. § 812 (b)(1)).

Marijuana has remained in Schedule I despite persistent efforts at re-scheduling since the 1970s by advocacy groups, such as NORML. Through petitions to the DEA, advocacy groups contend that marijuana does not fit the legal criteria for a Schedule I substance, owing to its purported medical uses and lack of high abuse liability.^{3,4,48} Another rescheduling petition, which was filed in 1995, is being evaluated by the FDA and DEA.

Availability for Research

To use marijuana for research purposes, researchers must register with the DEA, as well as adhere to other relevant requirements of the CSA and other federal statutes, such as the FD&C act. The National Institute on Drug Abuse (NIDA), one of the institutes of NIH, is the only organization in the United States licensed by the DEA to manufacture and distribute marijuana for research purposes. NIDA performs this function under its Drug Supply Program.[†] Through this program, NIDA arranges for marijuana, to be grown and processed through contracts with two organizations: the University of Mississippi and the Research Triangle Institute. The University of Mississippi grows, harvests, and dries marijuana; and the institute processes it into cigarettes. A researcher can obtain marijuana free of charge from NIDA through an NIH-approved research grant to investigate marijuana, or through a separate protocol review.³⁹ Research grant approvals are handled through the conventional NIH peer review

*Under the CSA, its only legal use is in research under strictly defined conditions.

†This is also the program through which several patients receive marijuana under a compassionate use program monitored by the FDA. For history and information on this effort, see Randall (1993).⁴⁸

process for extramural research, a highly competitive process with a success rate in 1997 of 32% of approved NIDA grants.⁴¹ Through the separate protocol review, in which a researcher funds research independently of an NIH grant, NIDA submits the researcher's protocol to several external reviewers who evaluate the protocol on the basis of scientific merit and relevance to the mission of NIDA and NIH.

Through those two avenues marijuana has been supplied to several research groups—most of those that apply. While there has been much discussion of NIDA's alleged failure to supply marijuana for research purposes, we are unaware of recent cases in which they failed to supply marijuana to an investigator with an NIH-approved grant for research on marijuana. Donald Abrams's difficulty in obtaining research funding and marijuana from NIDA has been much discussed,² but the case of a single individual should not be presumed to be representative of the community of marijuana researchers. Failure of investigators who apply to NIH for marijuana research grants to receive funding is hardly exceptional: in 1998 less than 25% of *all* first-time investigator-initiated grant applications (known as RO1s) to the NIH were funded.³⁸

To import marijuana under the CSA for research purposes, the procedures are more complex. Under DEA regulations, marijuana can be imported, provided that the researcher is registered with the DEA, has approval for marijuana research (21 CFR § 1301.11, .13, and .18), and has a DEA-approved permit for importation (21 CFR § 1312.11, .12, and .13), and that the exporter in the foreign country has appropriate authorization by the country of exportation. Importation would enable U.S. researchers to conduct research on marijuana grown by HortaPharm, a company that has developed unique strains of marijuana. However, no U.S. researcher has imported HortaPharm's marijuana because Dutch authorities have refused to issue an export permit, despite the issuance of an import permit by the DEA (D. Pate, HortaPharm, personal communication, 1998).*

HortaPharm, which is in the Netherlands, grows marijuana as a raw material for the manufacture of pharmaceuticals. Through selective breeding and controlled production, HortaPharm has developed marijuana strains that feature single cannabinoids, such as THC or cannabidiol. The plants contain a consistently "clean" phytochemical profile and a higher

*It might eventually be possible to import HortaPharm's marijuana from England, where HortaPharm is growing its marijuana strains for research use in clinical trials for multiple sclerosis (Boseley, 1998).¹⁰ England, as the country of origin, would have to provide appropriate authorization for export of the strains to the United States. Permission to export for research purposes is part of the basis for HortaPharm's participation in this project with GW Pharmaceuticals through a special set of licenses with the British Home Office (David Pate, HortaPharm, personal communication, 1998).

concentration of THC (16%) or other desired cannabinoids than seized marijuana. Marijuana seized in the United States in 1996 had a THC content averaging about 5%.¹⁶ Consistency of THC content is desirable because it overcomes the natural variability due to latitude, weather, and soil conditions. Product consistency is a basic tenet of pharmacology because it enables standardized dosing for regulatory and treatment purposes.

The difficulties of conducting research on marijuana were noted in the 1997 NIH report⁴⁰ that recommended that NIH facilitate clinical research by developing a centralized mechanism to promote design, approval, and conduct of clinical trials.

Regulatory Hurdles to Market

For marijuana to be marketed legally in the United States, a sponsor with sufficient resources would be obliged to satisfy the regulatory requirements of both the FD&C act and the CSA.

Under the FD&C act, a botanical product like marijuana *theoretically* might be marketed in oral form as a dietary supplement;* however, as a practical matter, only a new drug approval is likely to satisfy the provisions of the CSA, which require prescribing and distribution controls on drugs of abuse that also have an “accepted medical use.” (The final paragraphs of this section clarify the criteria for “accepted medical use.”)

Bringing marijuana to market as a new drug is uncharted terrain. The route is fraught with uncertainty for at least three pharmacological reasons: marijuana is a botanical product, it is smoked, and it is a drug with abuse potential. In general, botanical products are inherently more difficult to bring to market than are single chemical entities because they are complex mixtures of active and inactive ingredients. Concerns arise about product consistency, potency of the active ingredients, contamination, and stability of both active and inactive ingredients over time. These are among the concerns that a sponsor would have to overcome to meet the requirements for an NDA, especially those related to safety and to chemistry, manufacturing, and control.

A handful of botanical preparations are on the market, but none received formal approval as a new drug by today’s standards of safety and efficacy (FDA, Center for Drug Evaluation and Research, personal communication, 1998). The three marketed botanical preparations are older drugs that came to market years before safety and efficacy studies were required by legislative amendments in 1938 and 1962, respectively.

*Inhaled products may not lawfully be marketed as dietary supplements.

One of the botanical preparations is the prescription product digitalis. Because it came to market before 1938, it is available today, having been “grandfathered” under the law; but it does not necessarily meet contemporary standards for safety and effectiveness.²⁰ Two other botanical preparations, psyllium and senna, came to market between 1938 and 1962. Drugs entering the market during that period were later required to be evaluated by the FDA in what is known as the over-the-counter drug review process,²⁰ through which psyllium and senna were found to be generally recognized as safe and effective and so were allowed to remain on the market as over-the-counter drugs.* Although no botanical preparations have been approved as new drugs, it is important to point out that a number of individual plant constituents, either extracted or synthesized *de novo*, have been approved (for example, taxol and morphine). But these drug approvals were for single constituents rather than botanical preparations themselves. The FDA is developing guidance for industry to explain how botanicals are reviewed as new drugs, but the final document might not be available before 1999.

That marijuana is smoked might pose an even greater regulatory challenge. The risks associated with smoking marijuana are described in chapter 2. The FDA would have to weigh those risks with marijuana’s therapeutic benefits to arrive at a judgment about whether a sponsor’s NDA for marijuana met the requirements for safety and efficacy under the FD&C act. Marijuana delivered in a novel way that avoids smoking would overcome some, but not all, of the regulatory concerns. Vaporization devices that permit inhalation of plant cannabinoids without the carcinogenic combustion products found in smoke are under development by several groups; such devices would also require regulatory review by the FDA.

The regulatory hurdles to market posed by the CSA are formidable but not insurmountable. If marijuana received market approval as a drug by the FDA, it would most likely be rescheduled under the CSA, as was the case for dronabinol. That is because a new drug approval satisfies the “accepted medical use” requirement under the CSA for manufacture and distribution in commerce.¹³ But a new drug approval is not the *only* means to reschedule marijuana under the CSA.¹⁴ For years advocates for rescheduling have argued that marijuana does enjoy “accepted medical use,” even in the absence of a new drug approval. Although advocates have been unsuccessful in rescheduling efforts, their actions prompted

*Over-the-counter monographs for these products have been issued as tentative final monographs (proposed rules) but have not yet been issued in final form as final rules (FDA, Center for Drug Evaluation and Research, personal communication, 1998).

the DEA to specify the criteria by which it would determine whether a substance had “accepted medical use.” In the DEA’s 1992 denial of a re-scheduling petition, it listed these elements as constituting “accepted medical use”: the drug’s chemistry must be known and reproducible, there must be adequate safety studies, there must be adequate and well-controlled studies proving efficacy, the drug must be accepted by qualified experts, and the scientific evidence must be widely available.¹⁴

Assuming that all of those criteria were satisfied, marijuana could be rescheduled—but into which schedule? The level of scheduling would be dictated primarily by a medical and scientific recommendation to the DEA made by the secretary of DHHS.* As noted earlier, this recommendation is determined by the five scheduling criteria listed in the CSA. However, scheduling in a category less restrictive than Schedule II might be prohibited by international treaty obligations. The Single Convention on Narcotic Drugs, a treaty ratified by the United States in 1967, restricts scheduling of the plant and its resin to at least Schedule II (the more restrictive Schedule I is another option).¹³

Market Outlook

The market outlook for the development of marijuana as a new drug, on the basis of the foregoing analysis, is not favorable, for a host of scientific, regulatory, and commercial reasons. From a scientific point of view, research is difficult because of the rigors of obtaining an adequate supply of legal, standardized marijuana for study. Further scientific hurdles are related to satisfying the exacting requirements for FDA approval of a new drug. The hurdles are even more exacting for a botanical product because of the inherent problems with, for example, purity and consistency. Finally, the health risks associated with smoking pose another barrier to FDA approval unless a new smoke-free route of administration is demonstrated to be safe. Depending on the route of administration, an additional overlay of regulatory requirements might have to be satisfied.

From a commercial point of view, uncertainties abound. The often-cited cost of new drug development, about \$200–\$300 million, might not apply, but there are probably additional costs needed to satisfy the FDA’s requirements for a botanical product. As noted above, no botanical products have ever been approved as new drugs by the FDA under today’s stringent standards for safety and efficacy. Satisfying the legal require-

*At present, there is no practical mechanism for generating such a recommendation outside the new drug approval process, although such a mechanism could, theoretically, be developed.³³

ments of the CSA also will add substantially to the cost of development. On the positive side, so much research already has been done that some development costs will be lower. The cost of bringing dronabinol to market, for example, was reduced dramatically as a result of clinical trials supported with government funding. Nevertheless, it is impossible to estimate the cost of developing marijuana as a new drug. Estimating return on investment is similarly difficult. A full-fledged market analysis would be required for the indication being sought. Such an analysis would take into account the market limitations resulting from drug scheduling restrictions, stigma, and patentability.

The plant does not constitute patentable subject matter under U.S. patent law because it is unaltered from what is found in nature. So-called products of nature are not generally patentable.²⁸ New marijuana strains, however, could be patentable in the United States under a product patent or a plant patent because they *are* altered from what is found in nature. (A product patent prohibits others from manufacturing, using, or selling each strain for 20 years; a plant patent carries somewhat less protection.) HortaPharm has not yet sought any type of patent for its marijuana strains in the United States, but it has received approval for a plant registration in Europe (David Watson, HortaPharm, personal communication, 1998).

In short, development of the marijuana plant is beset by substantial scientific, regulatory, and commercial obstacles and uncertainties. The prospects for its development as a new drug are unfavorable unless return on investment is not a driving force. It is noteworthy that no pharmaceutical firm has sought to bring it to market in the United States. The only interest in its development appears to be in England in a small pharmaceutical firm (see Boseley, 1998¹⁰) and in the United States among physicians without formal ties to pharmaceutical firms (D. Abrams, University of California at San Francisco, and E. Russo, Western Montana Clinic, personal communications, 1998).

CONCLUSIONS

Cannabinoids are an interesting group of compounds with potentially far-reaching therapeutic applications. There is a surge of scientific interest in their development as new drugs, but the road to market for any new drug is expensive, long, risky, and studded with scientific, regulatory, and commercial obstacles. Experience with the only approved cannabinoid, dronabinol, might not illuminate the pathway because of the government's heavy contribution to research and development, dronabinol's scheduling history, and its small market.

There appear to be only two novel cannabinoids actively being developed for human use, but they have yet to be tested in humans in the

United States. Their experience is likely to be more predictive of the marketing prospects for other cannabinoids. It is too early to forecast the prospects for cannabinoids, other than to note that their development at this point is considered to be especially risky, to judge by the paucity of products in development and the small size of the pharmaceutical firms sponsoring them.

The market outlook in the United States is distinctly unfavorable for the marijuana plant and for cannabinoids found in the plant. Commercial interest in bringing them to market appears nonexistent. Cannabinoids in the plant are automatically placed in the most restrictive schedule of the Controlled Substances Act, and this is a substantial deterrent to development. Not only is the plant itself subject to the same scheduling strictures as are individual plant cannabinoids, but development of marijuana also is encumbered by a constellation of scientific, regulatory, and commercial impediments to availability.

REFERENCES

1. Abrahamov A, Abrahamov A, Mechoulam R. 1995. An efficient new cannabinoid antiemetic in pediatric oncology. *Life Sciences* 56:2097–2102.
2. Abrams DI. 1998. Medical marijuana: Tribulations and trials. *Journal of Psychoactive Drugs* 30:163–169.
3. AMA (American Medical Association Council on Scientific Affairs). 1997. *Report to the AMA House of Delegates*. Chicago: AMA.
4. Annas GJ. 1997. Reefer madness—the federal response to California’s medical-marijuana law. *The New England Journal of Medicine* 337:435–439.
5. Arno PS, Bonuck K, Davis M. 1995. Rare diseases, drug development, and AIDS: The impact of the Orphan Drug Act. *Milbank Quarterly* 73:231–252.
6. Asbury C. 1991. The Orphan Drug Act: The first seven years. *Journal of the American Medical Association* 265:893–897.
7. Atlantic Pharmaceuticals. 1997. Atlantic Pharmaceuticals’ proprietary compound shows promising anti-inflammatory effects in pre-clinical trials [WWW document]. URL <http://www.atlan.com/p-11-10-97ct3zurier.htm> (accessed September 1998).
8. Beal JE, Olson RLL, Morales JO, Bellman P, Yangco B, Lefkowitz L, Plasse TF, Shepard KV. 1995. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *Journal of Pain and Symptom Management* 10:89–97.
9. Beal JE, Olson R, Lefkowitz L, Laubenstein L, Bellman P, Yangco B, Morales JO, Murphy R, Powderly W, Plasse TF, Mosdell KW, Shepard KV. 1997. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. *Journal of Pain and Symptom Management* 14:7–14.
10. Boseley S. 1998. Multiple sclerosis victims to test medicinal effects of marijuana [WWW document]. URL <http://www.anomalous-images/news/news/227.HTML> (accessed September 8, 1998).

11. Bouaboula M, Perrachon S, Milligan L, Canat X, Rinaldi-Carmona M, Portier MB, Calandra B, Pecceu F, Lupker J, Maffrand JP, Le Fur G, Casellas P. 1997. A selective inverse agonist for central cannabinoid receptor inhibits mitogen-activated protein kinase activation stimulated by insulin or insulin-like growth factor 1. Evidence for a new model of receptor/ligand interactions. *Journal of Biological Chemistry* 272:22330–22339.
12. Calhoun, SR, Galloway GP, Smith DE. 1998. Abuse potential of dronabinol (Marinol). *Journal of Psychoactive Drugs* 30:187–196.
13. Cooper RM. 1980. Therapeutic use of marijuana and heroin: The legal framework. *Food Drug Cosmetic Law Journal* 35:68–82.
14. DEA (Drug Enforcement Administration). 1992. Marijuana scheduling petition; denial of petition; remand. *Federal Register* 57:10499–10508.
15. DEA. 1998. Drugs of abuse [WWW document]. URL <http://www.usdoj.gov/dea/pubs/abuse/contents.htm> (accessed September 1998).
16. DEA. 1996. The National Narcotics Intelligence Consumers Committee (NNICC) report [WWW document]. URL www.usdoj.gov/dea/pubs/intel/nnicc97.htm (accessed September 1998).
17. DEA. 1998b. Rescheduling of synthetic dronabinol from Schedule II to Schedule III. *Federal Register* 63:59751–59753.
18. DiMasi JA, Brown JS, Lasagna L. 1996. An analysis of regulatory review times of supplemental indications for already-approved drugs: 1989–1994. *Drug Information Journal* 30:315–337.
19. DiMasi JA, Hanson RW, Grabowski HG, Lasagna L. 1995. Research and development costs for new drugs by therapeutic category: A study of the U.S. pharmaceutical industry. *PharmacoEconomics* 7:152–169.
20. FDA (Food and Drug Administration). 1990. *From Test Tube to Patient: New Drug Development in the United States*. Rockville, MD: U.S. Department of Health and Human Services.
21. FDA. 1997b. *Draft Guidelines for Research Involving the Abuse Liability Assessment of New Drugs*. Rockville, MD: U.S. Department of Health and Human Services. Division of Anesthetic, Critical Care and Addiction Drug Products.
22. FDA. 1997a. Center for Drug Evaluation and Research Fact Book [WWW document]. URL <http://www.fda.gov/cder/homepage> (accessed September 1998).
23. FDA. 1998a. Center for Drug Evaluation and Research Handbook [WWW document]. URL <http://www.fda.gov/cder/handbook.htm> (accessed September 1998).
- 24a. FDA. 1998b. FDA proposes rules for dissemination information on off label uses (press release, June 5). Washington, DC: U.S. Department of Health and Human Services.
24. FDA. 1998c. Guidance for industry: Providing clinical evidence of effectiveness for human drugs and biological products. Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. May 1998 [WWW document]. URL <http://www.fda.gov/cder/guidance/1397fnl.pdf> (accessed September 1998).
25. FDA. 1998d. Office of Orphan Products Development Program Overview [WWW document]. URL <http://www.fda.gov/orphan/DESIGNAT/recent.htm> (accessed October 14, 1998).
26. Felder CC, Glass M. 1998. Cannabinoid receptors and their endogenous agonists. *Annual Reviews of Pharmacology and Toxicology* 38:179–200.
27. Glain SJ. 1998. I. *Wall Street Journal*.
28. Gollin MA. 1994. Patenting recipes from nature's kitchen: How can a naturally occurring chemical like taxol be patented? *Biotechnology (NY)* 12:406–407.

29. Hampson AJ, Grimaldi M, Axelrod J, Wink D. 1998. Cannabidiol and (-)-delta-9-tetrahydrocannabinol are neuroprotective antioxidants. *Proceedings of the National Academy of Sciences USA* 95:8268–8273.
30. Howlett AC. 1995. Pharmacology of cannabinoid receptors. *Annual Review of Pharmacology and Toxicology* 35:607–634.
31. IOM (Institute of Medicine). 1990. *Modern Methods of Clinical Investigation*. Washington, DC: National Academy Press.
32. IOM. 1991. *Expanding Access to Investigational Therapies for HIV Infection and AIDS*. Washington, DC: National Academy Press.
33. IOM. 1995. *The Development of Medications for the Treatment of Opiate and Cocaine Addictions: Issues for the Government and Private Sector*. Washington, DC: National Academy Press.
34. IOM. 1996. *Pathways of Addiction: Opportunities in Drug Abuse Research*. Washington, DC: National Academy Press.
35. Knoller N, Levi L, Israel Z, Razon N, Reichental E, Rappaport Z, Ehrenfreund N, Biegon A. Safety and outcome in a Phase II clinical trial of dexanabinol in severe head trauma. Congress of Neurological Surgeons Annual Meeting. Seattle, WA, Oct. 7, 1998.
36. Mechoulam R, Hanus L, Fride E. 1998. Towards cannabinoid drugs—revisited. In: Ellis GP, Luscombe DK, Oxford AW, Editors, *Progress in Medicinal Chemistry*. vol. 35. Amsterdam: Elsevier Science. Pp. 199–243.
37. Nainggolan L. 1997. Marijuana—a missed market opportunity? *Scrip Magazine*.
38. National Institutes of Health (NIH). 1999. <http://www.nih.gov/grants/award/award.htm>.
39. NIDA (National Institute on Drug Abuse). 1996. *Research Resources: Drug Supply System, 10th Edition*. Rockville, MD.
40. NIH (National Institutes of Health). 1997. Workshop on the Medical Utility of Marijuana. Report to the Director, National Institutes of Health by the Ad Hoc Group of Experts. Bethesda, MD, February 19–20, 1997. Bethesda, MD: National Institutes of Health.
41. NIH. 1998. FY (1970–1997 NIH (Preliminary) competing research project applications [WWW document]. URL <http://silk.nih.gov/public/cbz2rfm.@www.comic.dsncc> (accessed October 1998).
42. Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. 1980. Plasma delta-9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clinical Pharmacology and Therapeutics* 28:409–416.
43. OTA (Office of Technology Assessment). 1991. *Biotechnology in a Global Economy*. OTA-BA-494. Washington, DC: U.S. Government Printing Office.
44. OTA. 1993. *Pharmaceutical R&D: Costs, Risks and Rewards*. OTA-H-522. Washington, DC: U.S. Government Printing Office.
45. PDR (Physicians' Desk Reference). 1996. *Physicians' Desk Reference*. 50th ed. Montvale, NJ: Medical Economics Co.
46. Pertwee RG. 1997. Cannabis and cannabinoids: Pharmacology and rationale for clinical use. *Pharmaceutical Science* 3:539–545.
47. Plasse TF, Gorter RW, Krasnow SH, Lane M, Shepard KV, Wadleigh RG. 1991. Recent clinical experience with dronabinol. *Pharmacology Biochemistry and Behavior* 40:695–700.
48. Randall IV B. 1993. *Medical Use of Marijuana: Policy and Regulatory Issues*. 93-308 SPR. Washington, DC: Congressional Research Service.

49. Schmidt WK. 1998. Overview of current investigational drugs for the treatment of chronic pain. National Managed Health Care Congress, Second Annual Conference on Therapeutic Developments in Chronic Pain. Annapolis, MD, May 18, 1998.
50. Shapiro RS. 1994. Legal bases for the control of analgesic drugs. *Journal of Pain and Symptom Management* 9:153–159.
51. Shen M, Piser TM, Seybold VS, Thayer SA. 1996. Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. *Journal of Neuroscience* 16:4322–4334.
52. Shohami E, Weidenfeld J, Ovadia H, Vogel Z, Hanus L, Fride E, Breuer A, Ben-Shabat S, Sheskin T, Mechoulam R. 1996. Endogenous and synthetic cannabinoids: Recent advances. *CNS Drug Reviews* 2:429–451.
53. Spilker B. 1989. *Multinational Drug Companies: Issues in Drug Discovery and Development*. New York: Raven Press.
54. Standaert DG, Young AB. 1996. Treatment of central nervous system degenerative disorders. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RR, Gilman AG, Editors, *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*. 9th ed. New York: McGraw-Hill. Pp. 503–519.
55. Striem S, Bar-Joseph A, Berkovitch Y, Biegon A. 1997. Interaction of dexanabinol (HU-211), a novel NMDA receptor antagonist, with the dopaminergic system. *European Journal of Pharmacology* 388:205–213.
56. Timpone JG, Wright DJ, Li N, Egorin MJ, Enama ME, Mayers J, Galetto G, DATRI 004 Study Group. 1997. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. The DATRI 004 study group. *AIDS Research and Human Retroviruses* 13:305–315.
57. Turk DC, Brody MC, Akiko OE. 1994. Physicians' attitudes and practices regarding the long-term prescribing of opioids for non-cancer pain. *Pain* 59:201–208.
58. Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. 1997. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry* 12:913–919.
59. Voth EA, Schwartz RH. 1997. Medicinal applications of delta-9-tetrahydrocannabinol and marijuana. *Annals of Internal Medicine* 126:791–798.
60. Wall ME, Sadler BM, Brine D, Taylor H, Perez-Reyes M. 1983. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. *Clinical Pharmacology and Therapeutics* 34:352–363.
61. Zurier RB, Rossetti RG, Lane JH, Goldberg JM, Hunter SA, Burstein SH. 1998. Dimethylheptyl-THC-11 oic acid: A non-psychoactive antiinflammatory agent with a cannabinoid template structure. *Arthritis and Rheumatism* 41:163–170.



Appendixes

APPENDIX A

Individuals and Organizations That Spoke or Wrote to the Institute of Medicine About Marijuana and Medicine

Donald I. Abrams
University of California at San
Francisco

Jill Aguilera
Colorado Federation of Parents

William F. Alden
D.A.R.E. America

Roger D. Anderson
Anderson Clinical Research

M. Douglas Anglin
UCLA Drug Abuse Research
Center

Dave Baleria
Jackson County Sheriff's Office

Joe Barker

Frank Bartosic
Minister of Universal Life
Church

Dana Beal
Cures Not Wars

J. Bellam
Center for Drug Information

Sandra S. Bennett
Northwest Center for Health and
Safety

Anna T. Boyce
California Senior Legislature
(Prop 215)

William Britt

Richard Brookhiser
National Review

Ronald Brooks
California Narcotic Officers
Association

Bonnie Broussard
L.A. Takes a Stand, Inc.

Al Byrne
Patients Out of Time

Marvin Edward Chavez, Sr.
O.C. Patient-Doctor-Nurse
Support Group Cannabis
Co-Op

Steven Childers
Bowman Gray School of
Medicine
Wake Forest University

Barb Christensen
Prevention Partners

Gale Cincotta
National People's Action

Carol Coburn
Prevention Partners

Chris Conrad
Author of Hemp for Health

Paul Consroe
University of Arizona

J. Richard Crout
Private Consultant

Judy Cushing
Oregon Partnership, National
Family Partnership

John De Miranda
Peninsula Health Concepts

Mahendra Dedhiya
Roxane Laboratories, Inc.

Robert Deitch
Cannabis Freedom Fund

Philip Diaz
Physicians for Prevention

Stephen L. Dilts
American Academy of Addiction
Psychiatry

Rick Doblin
MAPS and Kennedy School of
Government

Del Dolton

Barbara Douglass
Drug-Free Youth—USA

Robert Dudley
UNIMED

Victoria Duran
National Parents and Teachers
Association

David Edwards

Edward Ehman
Certified Prevention Specialist

Mahmoud ElSohly
University of Mississippi

Mouncey Ferguson

Howard L. Fields
University of California at San
Francisco

Jody Fitt

Richard W. Foltin
Columbia University

Etienne Fontan
Cannabis Alliance of Veterans,
1st CAV

Meg Foster

Phyllis Gardner
ALZA Corporation

Charles V. Giannasio
American Academy of Addiction
Psychiatry

Dale Gieringer
California NORML, Friends of
215

Mark Gold
University of Florida Brain
Institute

Richard Gralla
OCHSNER Cancer Institute

Linda Hall
Pride, Omaha, Inc.

Margaret Haney
Columbia University

Ann Hansen
Michigan Communities in Action
for Drug-Free Youth

Jim Hardin

Terry Hensley
Drug-Free America Foundation

Kimberly Hessel
American Cancer Society and
Muscatine General Hospital

Michele Hodak
National Education Association

Leo Hollister
Harris County Psychiatric Center

Jennifer Hudson
Oregonians Against Dangerous
Drugs

Paul Isford

Becki Jelinek
Family Service/South Omaha
Counseling

Jeffery Jones
Oakland Cannabis Buyers'
Cooperative

Linda R. Wolf Jones
Therapeutic Communities of
America

Norbert E. Kaminski
Michigan State University

Robert Kampia
Marijuana Policy Project

Paul L. Kaufman
University of Wisconsin Medical
School

Andrew Kinnon

Thomas Klein
University of South Florida
College of Medicine

Audra Koerber
Orange County Patient, Doctor,
Nurse Support Group

Ellen Komp
San Luis Obispo Citizens for
Medical Marijuana

Billy R. Martin
Virginia Commonwealth
University

George Koob
Scripps Research Institute

Mary Lynn Mathre
Patients Out of Time

Thomas R. Kosten
American Academy of Addiction
Psychiatry

Jeane McCarty
West Coast Neonatology

Donald Kotler
St. Luke's-Roosevelt Hospital

Todd McCormick

Michael Krawitz
Disabled American Veterans,
American Legion

JoAnna McKee
Green Cross Patient Co-Op

Kiyoshi Kuromiya
Critical Path AIDS Project

Manon McKinnon
Empower America

Karin Kyles
Connecticut Communities for
Drug-Free Youth, Inc.

George McMahan

Peter McWilliams

Eric Larson
University of Washington
Medical Center

John Edward Mendelson
University of California at
San Francisco

Bonnie Metcalf
Yuba County Compassionate Use
Co-Op

Linda B. Ledger
O. J. Federation for Drug-Free
Communities

R. Mikin
American Academy of Addiction
Psychiatry

Carla Lowe

Alan D. Miller
The Rockefeller University

Ray Lozano
C.A.D.F.Y.

Jim Montgomery

Patrick Magee
Orange County Hemp Council

John P. Morgan
City University of New York
Medical School

Robert L. Maginnis
Family Research Council

Arlene Munoz
Office of Substance Abuse,
San Joaquin County

Stephen Popolizio
The International Association of
Lions Clubs

Elvy Musikka

Jo Prang
NFP Networker (Oregon
Partnership)
Adolescent Substance Abuse
Prevention, Inc./MEDICAP
Pharmacy

Richard E. Musty
University of Vermont

Edgar P. Nace
American Academy of Addiction
Psychiatry

Beny Primm
Addiction Research and
Treatment Corporation

Joyce Nalepka
America Cares

Carol Reeves
Greenville Family Partnership

Tammera Nauts
Great Falls Public Schools

Irvin Rosenfeld
Stockbroker

Dan Noelle
Multnomah County Sheriff

Michael Rowbotham
University of California at
San Francisco

Stephen O'Brien
East Bay Aids Center

A. Kenison Roy
American Society of Addiction

Jerry Olli
Michigan Elks and Michigan
Communities in Action for
Drug-Free Youth

Reid Rubsamen
Aradigm

Lynn Osburn
Access Unlimited

Sue Rusche
National Families in Action

Robert Pandina
Rutgers, The State University of
New Jersey

Clara Sanudo-Pena
Brown University

David Pate
HortaPharm B.V.

Peggy Sapp
Informed Families

Maggie Petito
Drug Watch International

C. Robert Schuster
Wayne State University School of
Medicine

Greg Scott

Richard Scribner
Louisiana State University
Medical School

Betty S. Sembler
S.O.S.

Richard W. Sharke
McDowell Drug Task Force/
CADCA

Lynette Shaw
Marin Alliance for Medical
Marijuana

John Sheridan
New York City Marijuana
Buyers' Club

Cathy Shipp
PRIDE-Omaha, Inc.

Stephen Sidney
Kaiser Permanente

Brian Slater

Kenneth Smuland
Women's Alliance for Medical
Marijuana

Mark Stone
Washington, D.C., Police
Department

Barb Sweeney
Flower Therapy

Donald Tashkin
University of California at Los
Angeles School of Medicine

Dana Taub

Chuck Thomas
Marijuana Policy Project
Foundation

Bill Tiuem
Gainesville Family Partnership

Joyce Tobias
Parents' Association to
Neutralize Drug and Alcohol
Abuse, Inc.

Jeanne Trumble
American Academy of Addiction
Psychiatry

Barbara Urist-Fenton
OCHC

Eric A. Voth
International Drug Strategy
Institute

Michelle Voth
Kansas Family Partnership

C. Gary Wainwright
American Civil Liberties Union

J. Michael Walker
Brown University

Gene Weeks
Southern California Medical
Cannabis Consumers' Co-Op

Sandra Welch
Medical College of Virginia

Tracy Wells
Family Service–Healthy
Alternatives for Little Ones

Sgt. Larry L. Welty
Oregon State Police

Sis Wenger
National Association of Children
of Alcoholics

Lennice Werth
Virginians Against Drug
Violence

Casey Wilbanks
Green Cross

Carol Wortman
Drug Watch Pennsylvania

Kevin Zeese
Common Sense for Drug Policy

APPENDIX B

Workshop Agendas

Workshop on Perspectives on the Medical Use of Marijuana: Basic and Clinical Science

December 14–16, 1997
Beckman Center, Irvine, California

AGENDA

Sunday, December 14, 1997

- 2:00 p.m. Introduction
Constance Pechura, *IOM Division Director*,
Neuroscience and Behavioral Health
- 2:30 p.m. Public Input Session, *5 minutes per person*
Moderator: Stanley Watson, Jr., *IOM Study Investigator*,
University of Michigan
- 5:30 p.m. ADJOURN

Monday, December 15, 1997

CANNABINOID NEUROSCIENCE

- 8:30 a.m. **Moderator:** Stanley Watson, *IOM Study Investigator*,
University of Michigan
- 8:45 a.m. **Neuropharmacology of Cannabinoids and Their Receptors**
Steven R. Childers, Wake Forest University School of
Medicine
- 9:15 a.m. **Precipitated Cannabinoid Withdrawal and Sensory
Processing of Painful Stimuli**
J. Michael Walker, Brown University
- 9:45 a.m. **Role of Cannabinoids in Movement**
Clara Sanudo, Brown University
- 10:15 a.m. **Tolerance and Cannabinoid-Opioid Interactions**
Sandra P. Welch, Medical College of Virginia
- 10:45 a.m. BREAK
- MEDICAL USES OF MARIJUANA:
CLINICAL DATA AND BASIC BIOLOGY
- 11:10 a.m. **Moderator:** John A. Benson, Jr., *IOM Study Investigator*,
Oregon Health Sciences University
- 11:15 a.m. **Profile of Medical Marijuana Users**
John Mendelson, University of California at San Francisco
- 11:45 a.m. **Immune Modulation by Cannabinoids**
Norbert Kaminski, Michigan State University
- 12:15 p.m. **Psychological Effects of Marijuana Use**
Charles R. Schuster, Wayne State University
- 12:45 p.m. LUNCH

- 1:45 p.m. **Marijuana and Glaucoma**
 Paul Kaufman, University of Wisconsin
- 2:15 p.m. **Effects of Marijuana and Cannabinoids in Neurological Disorders**
 Paul Consroe, University of Arizona Health Sciences Center
- 2:45 p.m. **Neural Mechanisms of Cannabinoid Analgesia**
 Howard Fields, University of California at San Francisco
- 3:15 p.m. **Pain Management**
 Michael Rowbotham, University of California at San Francisco
- 3:45 p.m. **Wasting Syndrome Pathogenesis and Clinical Markers**
 Donald Kotler, St. Luke's-Roosevelt Hospital
- 4:15 p.m. **Clinical Experience with Marijuana**
 Stephen O'Brien, East Bay AIDS Center
- 4:45 p.m. ADJOURN

Tuesday, December 16, 1997

MEDICAL USES OF MARIJUANA:
 CLINICAL DATA AND BASIC BIOLOGY

- 8:30 a.m. **Moderator:** John A. Benson, Jr., *IOM Study Investigator*,
 Oregon Health Sciences University
- 8:45 a.m. **Marijuana in AIDS Wasting: Tribulations and Trials**
 Donald I. Abrams, University of California at San Francisco
- 9:15 a.m. **Nausea and Vomiting: Underlying Mechanisms and Upcoming Treatments**
 Alan D. Miller, The Rockefeller University
- 9:45 a.m. **Postchemotherapy Nausea and Antiemetics**
 Richard J. Gralla, Ochsner Cancer Center

10:15 a.m. BREAK

SUMMARY VIEWS

10:30 a.m. **Marijuana Is Different from THC: A Review of Basic Research and State Studies of Antiemesis**

Richard E. Musty, University of Vermont

11:00 a.m. **Medical Uses of Crude Marijuana: Medical and Social Issues**

Eric A. Voth, The International Drug Strategy Institute

11:30 a.m. **General Questions**

Moderator: John A. Benson, Jr., *IOM Study Investigator*

12:00 noon ADJOURN

**Workshop on
Acute and Chronic Effects of Marijuana Use**

January 22–23, 1998
New Orleans Marriott Hotel
New Orleans, Louisiana

AGENDA

Thursday, January 22, 1998

- 2:00 p.m. Introduction
Constance Pechura, *IOM Division Director*,
Neuroscience and Behavioral Health
- 2:30 p.m. Public Input Session, *5 minutes per person*
Moderator: Stanley Watson, Jr., *IOM Study Investigator*,
University of Michigan
- 4:30 p.m. ADJOURN

Friday, January 23, 1998

- 8:30 a.m. **Moderator:** John A. Benson, Jr., *IOM Study Investigator*,
Oregon Health Sciences University

HEALTH CONSEQUENCES OF MARIJUANA USE

- 9:00 a.m. **Health Consequences of Marijuana Use: Epidemiological Studies**
Stephen Sidney, Kaiser Permanente, Oakland, CA
- 9:30 a.m. **Immunity, Infections, and Cannabinoids**
Thomas Klein, University of South Florida
- 10:00 a.m. **Pulmonary Effects of Smoked Marijuana**
Donald Tashkin, University of California at Los Angeles
- 10:30 a.m. BREAK

10:45 a.m. **Is Marijuana Carcinogenic?: Epidemiological and Biological Evidence**

Panel Discussion

Stephen Sidney
Donald Tashkin

12:00 noon LUNCH

EFFECTS OF MARIJUANA ON BEHAVIOR

1:30 p.m. **Marijuana: Addictive and Amotivational States, the Scientific Evidence**

John Morgan, City University of New York Medical School

2:00 p.m. **Marijuana's Acute Behavioral Effects in Humans**

Richard Foltin, Columbia University

2:30 p.m. **Tolerance and Dependence Following Chronic Administration of Oral THC or Smoked Marijuana to Humans**

Margaret Haney, Columbia University

3:00 p.m. **Patterns of Continuity and Discontinuity of Marijuana Use in Relationship to Other Drugs**

Robert Pandina, Rutgers University

3:30 p.m. ADJOURN

Workshop on Prospects for Cannabinoid Drug Development

February 23–24, 1998
 National Academy of Sciences Building
 Washington, D.C.

AGENDA

Monday, February 23, 1998

- 1:30 p.m. Introduction
 Constance Pechura, *IOM Division Director*,
 Neuroscience and Behavioral Health
- 2:00 p.m. Public Input Session, *5 minutes per person*
 Moderator: John A. Benson, Jr., *IOM Study Investigator*,
 Oregon Health Sciences University
- 5:30 p.m. ADJOURN

Tuesday, February 24, 1998

- 8:30 a.m. Introduction
 Constance Pechura, *IOM Division Director*
 Neuroscience and Behavioral Health
- Moderator:** Stanley J. Watson, Jr., *IOM Study Investigator*,
 University of Michigan

OVERVIEWS OF PRECEDING WORKSHOPS

- 8:45 a.m. **Acute and Chronic Effects of Marijuana**
 Billy R. Martin, Medical College of Virginia
- 9:25 a.m. **Perspectives on the Medical Use of Marijuana**
 Eric B. Larson, University of Washington Medical School
- 9:55 a.m. **The Neurobiology of Cannabinoid Dependence**
 George F. Koob, Scripps Research Institute
- 10:25 a.m. BREAK

DRUG DEVELOPMENT

10:45 a.m. **Regulatory Requirements Affecting Marijuana**

J. Richard Crout, Crout Consulting

11:15 a.m. **Marinol and the Market**

Robert E. Dudley, Unimed Pharmaceuticals, Inc.

11:45 a.m. **Development of Cannabis-based Therapeutics**

Dave Pate, HortaPharm, B.V.

12:15 p.m. LUNCH

DRUG DELIVERY

1:30 p.m. **Alternative Drug Delivery Technologies for the
Therapeutic Use of Marijuana**

Phyllis I. Gardner, ALZA Corporation, Stanford University

2:00 p.m. **Delivery of Analgesics via the Respiratory Track**

Reid M. Rubsamen, Aradigm Corporation

2:30 p.m. **Current Concepts for Delivery of THC**

Mahendra G. Dedhiya, Roxanne Laboratories, Inc.

3:00 p.m. **Δ^9 -THC-Hemisuccinate in Suppository Formulation:
An Alternative to Oral and Smoked THC**

Mahmoud A. ElSohly, University of Mississippi,
ElSohly Laboratories, Inc.

3:30 p.m. **Concluding Remarks**

John A. Benson, Jr., *IOM Study Investigator*,
Oregon Health Sciences University

3:45 p.m. ADJOURN

APPENDIX C

Scheduling Definitions

SCHEDULING DEFINITIONS ESTABLISHED BY THE CONTROLLED SUBSTANCES ACT OF 1970

Schedule I (includes heroin, LSD, and marijuana)

- (A) The drug or other substance has a high potential for abuse.
- (B) The drug or other substance has no currently accepted medical use in treatment in the United States.
- (C) There is a lack of accepted safety for the use of the drug or other substance under medical supervision.

Schedule II (includes Marinol, methadone, morphine, methamphetamine, and cocaine)

- (A) The drug or other substance has a high potential for abuse.
- (B) The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.
- (C) Abuse of the drug or other substances may lead to severe psychological or physical dependence.

Schedule III (includes anabolic steroids)

- (A) The drug or other substance has a potential of abuse less than the drugs or other substances in Schedules I and II.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States.

(C) Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.

Schedule IV (includes Valium and other tranquilizers)

(A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule III.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States.

(C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.

Schedule V (includes codeine-containing analgesics)

(A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule IV.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States.

(C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule IV.

SOURCES: LeCraw (1996) and 21 U.S.C. 812.

APPENDIX D

Statement of Task

The study will assess what is currently known and not known about the medical use of marijuana. It will include a review of the science base regarding the mechanism of action of marijuana, an examination of the peer-reviewed scientific literature on the efficacy of therapeutic uses of marijuana, and the costs of using various forms of marijuana versus approved drugs for specific medical conditions (e.g., glaucoma, multiple sclerosis, wasting diseases, nausea, and pain).

The study will also include an evaluation of the acute and chronic effects of marijuana on health and behavior; a consideration of the adverse effects of marijuana use compared with approved drugs; an evaluation of the efficacy of different delivery systems for marijuana (e.g., inhalation vs. oral); an analysis of the data concerning marijuana as a gateway drug; and an examination of the possible differences in the effects of marijuana due to age and type of medical condition.

SPECIFIC ISSUES

Specific issues to be addressed fall under three broad categories: the science base, therapeutic use, and economics.

Science Base

- Review of neuroscience related to marijuana, particularly the relevance of new studies on addiction and craving.
- Review of behavioral and social science base of marijuana use, par-

ticularly assessment of the relative risk of progression to other drugs following marijuana use.

- Review of the literature determining which chemical components of crude marijuana are responsible for possible therapeutic effects and for side effects.

Therapeutic Use

- Evaluation of any conclusions on the medical use of marijuana drawn by other groups.
- Efficacy and side effects of various delivery systems for marijuana compared to existing medications for glaucoma, wasting syndrome, pain, nausea, or other symptoms.
- Differential effects of various forms of marijuana that relate to age or type of disease.

Economics

- Costs of various forms of marijuana compared with costs of existing medications for glaucoma, wasting syndrome, pain, nausea, or other symptoms.
- Assessment of the differences between marijuana and existing medications in terms of access and availability.

These specific areas along with the assessments described above will be integrated into a broad description and assessment of the available literature relevant to the medical use of marijuana.

APPENDIX E

Recommendations Made in Recent Reports on the Medical Use of Marijuana

Recommendations from five recent key reports pertaining to the medical use of marijuana are listed below by subject. Recommendations made on issues outside the scope of this report, such as drug law and scheduling decisions, are not included here. The following reports were reviewed:

- Health Council of the Netherlands, Standing Committee on Medicine. 1996. *Marihuana as Medicine*. Rijswijk, the Netherlands: Health Council of the Netherlands.
- *Report of the Council on Scientific Affairs*. 1997. Report to the American Medical Association House of Delegates. Subject: Medical Marijuana. Chicago: AMA.
- British Medical Association. 1997. *Therapeutic Uses of Cannabis*. United Kingdom: Harwood Academic Publishers.
- National Institutes of Health. 1997. *Workshop on the Medical Utility of Marijuana*. Bethesda, MD: National Institutes of Health.
- World Health Organization. 1997. *Cannabis: A Health Perspective and Research Agenda*. Geneva: WHO.

In November 1998, the British House of Lords Science and Technology Committee published *Medical Use of Cannabis*, in which the committee reported its conviction that “cannabis almost certainly does have genuine medical applications.” The House of Lords report was released too late in the preparation of the present Institute of Medicine report to per-

mit careful analysis and is not summarized here. It is available on the Internet at: *www.parliament.uk*.

GENERAL RECOMMENDATIONS

Health Council of the Netherlands

In order to assess the efficacy of marijuana and cannabinoids, the committee studied literature published during the past 25 years. Based on those findings, the committee concluded that there was insufficient evidence to justify the medical use of marijuana.

AMA House of Delegates

Adequate and well-controlled studies of smoked marijuana should be conducted in patients who have serious conditions for which preclinical, anecdotal, or controlled evidence suggests possible efficacy, including AIDS wasting syndrome, severe acute or delayed emesis induced by chemotherapy, multiple sclerosis, spinal cord injury, dystonia, and neuropathic pain.

British Medical Association

Research on the clinical indications for medical prescription of cannabinoids should be undertaken. For all indications listed below (antiemetics, pain, epilepsy, glaucoma, asthma, immunological effects, multiple sclerosis, spinal cord injury, and other spastic disorders) further research is required to establish suitable methods of administration, optimal dosage regimens, and routes of administration. A central registry should be kept of patients prescribed cannabinoids so that the effects can be followed up over the long term.

National Institutes of Health

For at least some potential indications, marijuana looks promising enough to recommend that new controlled studies be done. The indications in which varying levels of interest were expressed are the following: appetite stimulation and wasting, chemotherapy-induced nausea and vomiting, neurological and movement disorders, analgesia, [and] glaucoma. Until studies are done using scientifically acceptable clinical trial design and subjected to appropriate statistical analysis, the question concerning the therapeutic utility of marijuana will likely remain largely un-

answered. To the extent that the NIH can facilitate the development of a scientifically rigorous and relevant database, the NIH should do so.

World Health Organization

Therapeutic uses of cannabinoids warrant further basic pharmacological and experimental investigation and clinical research into their effectiveness. More research is needed on the basic neuropharmacology of THC and other cannabinoids so that better therapeutic agents can be found.

ANALGESIA

Health Council of the Netherlands

No recommendations made.

AMA House of Delegates

Controlled evidence does not support the view that THC or smoked marijuana offers clinically effective analgesia without causing significant adverse events when used alone. Preclinical evidence suggests that cannabinoids can potentiate opioid analgesia and that cannabinoids may be effective in animal models of neuropathic pain. Further research into the use of cannabinoids in neuropathic pain is warranted.

British Medical Association

The prescription of nabilone, THC, and other cannabinoids should be permitted for patients with intractable pain. Further research is needed into the potential of cannabidiol as an analgesic in chronic, terminal, and postoperative pain.

National Institutes of Health

Evaluation of cannabinoids in the management of neuropathic pain, including HIV-associated neuropathy, should be undertaken.

World Health Organization

No recommendations made, although the report notes that some newly synthesized cannabinoids are extremely potent analgesics; how-

ever, separation of the analgesia and side effects remains to be demonstrated.

NAUSEA AND VOMITING

Health Council of the Netherlands

No recommendations made.

AMA House of Delegates

THC and smoked marijuana are considerably less effective than currently available therapies to treat acute nausea and vomiting caused by chemotherapy, although certain patients still do not respond adequately to conventional therapy. Research involving THC and smoked marijuana should focus on their possible use in treating delayed nausea and vomiting and their adjunctive use in patients who respond inadequately to 5-HT₃ antagonists. The use of an inhaled substance has the potential to benefit ambulatory patients who are experiencing the onset of nausea and are thus unable to take oral medications.

British Medical Association

Further research is needed on the use of Δ^8 -THC as an antiemetic, the use of cannabidiol in combination with THC, and the relative effectiveness of cannabinoids compared with 5-HT₃ antagonists. Further research is needed in other cases, such as postoperative nausea and vomiting.

National Institutes of Health

Inhaled marijuana merits testing in controlled, double-blind, randomized trials for nausea and vomiting.

World Health Organization

More basic research on the central and peripheral mechanisms of the effects of cannabinoids on gastrointestinal function may improve the ability to alleviate nausea and emesis.

WASTING SYNDROME AND APPETITE STIMULATION

Health Council of the Netherlands

No recommendations made.

AMA House of Delegates

THC is moderately effective in the treatment of AIDS wasting, but its long duration of action and intensity of side effects preclude routine use. The ability of patients who smoke marijuana to titrate their dosage according to need and the lack of highly effective, inexpensive options to treat this debilitating disease create the conditions warranting formal clinical trials of smoked marijuana as an appetite stimulant in patients with AIDS wasting syndrome.

British Medical Association

Allowing the prescription of nabilone and THC for cancer chemotherapy and HIV/AIDS seems justified for preventing weight loss and treating anorexia in HIV/AIDS irrespective of whether the patient is experiencing nausea and/or vomiting.

National Institutes of Health

Areas of study for the potential appetite-stimulating properties of marijuana include the cachexia of cancer, HIV/AIDS symptomatology, and other wasting syndromes. Investigations should be designed to assess long-term effects on immunology status, the rate of viral replication, and clinical outcomes in participants as well as weight gain. In therapeutic trials of cachexia, research should attempt to separate out the effect of marijuana on mood versus appetite. Some questions need to be answered in the studies: (1) Does smoking marijuana increase total energy intake in patients with catabolic illness? (2) Does marijuana use alter energy expenditure? (3) Does marijuana use alter body weight and to what extent? (4) Does marijuana use alter body composition and to what extent?

World Health Organization

No specific recommendations are made, although the report notes that dronabinol is an effective appetite stimulant for patients with AIDS wasting syndrome.

MUSCLE SPASTICITY

Health Council of the Netherlands

No recommendations made.

AMA House of Delegates

Considerably more research is required to identify patients who may benefit from THC or smoked marijuana and to establish whether responses are primarily subjective in nature. A therapeutic trial of smoked marijuana or THC may be warranted in patients with spasticity who do not derive adequate benefit from available oral medications, prior to their considering intrathecal baclofen therapy or neuroablative procedures.

British Medical Association

A high priority should be given to carefully controlled trials of cannabinoids in patients with chronic spastic disorders that have not responded to other drugs are indicated. In the meantime, there is a case for the extension of the indications for nabilone and THC for use in chronic spastic disorders unresponsive to standard drugs.

National Institutes of Health

No recommendations are made, although the report notes that marijuana or the use of other cannabinoids as human therapies might be considered for treating spasticity and nocturnal spasms complicating multiple sclerosis and spinal cord injury.

World Health Organization

The report notes that cannabinoids have not yet been proven useful in treating multiple sclerosis, but therapeutic uses of cannabinoids are being demonstrated by controlled studies as an antispasmodic. Research in this area should continue.

MOVEMENT DISORDERS

Health Council of the Netherlands

No recommendations made.

AMA House of Delegates

Considerably more research is required to identify dystonic patients who may benefit from THC or smoked marijuana and to establish whether responses are primarily subjective in nature.

British Medical Association

The potential of (+)-HU-210 for neurodegenerative disorders should be explored through further research.

National Institutes of Health

No recommendations made, although the report notes that marijuana or the use of other cannabinoids as human therapies might be considered for treating for some forms of dystonia.

World Health Organization

No recommendations made, although the report notes that cannabinoids have not yet been proven useful in the treatment of movement disorders.

EPILEPSY**Health Council of the Netherlands**

No recommendations made.

AMA House of Delegates

No recommendations made.

British Medical Association

Trials with cannabidiol (which is nonpsychoactive), used to enhance the activity of other drugs in cases not well controlled by other anti-convulsants, are needed.

National Institutes of Health

No recommendations made, although the report notes that marijuana

or the use of other cannabinoids as human therapies might be considered for treating various active epilepsy states.

World Health Organization

No recommendations made, although the report notes that cannabinoids have not yet been proven useful in the treatment of convulsant disorders, but therapeutic uses of cannabinoids are being demonstrated by controlled studies as an anticonvulsant.

GLAUCOMA

Health Council of the Netherlands

No recommendations made.

AMA House of Delegates

Neither smoked marijuana nor THC is a viable approach in the treatment of glaucoma, but research on their mechanism of action may be important in developing new agents that act in an additive or synergistic manner with currently available therapies.

British Medical Association

Cannabinoids do not at present look promising for this indication, but much further basic and clinical research is needed to develop and investigate cannabinoids that lower intraocular pressure, preferably by topical application (e.g., eye drops, inhalant aerosols), without producing unacceptable systemic and central nervous system effects.

National Institutes of Health

Further studies to define the mechanism of action and to determine the efficacy of Δ^9 -tetrahydrocannabinol and marijuana in the treatment of glaucoma are justified. There does not appear to be any obvious reason to use smoked marijuana as a primary "stand-alone" investigational therapy, as there are many available agents for treatment, and these topical preparations seem to be potentially ideal. An approach that may be useful is to study smoked marijuana in incomplete responders to standard therapies. The suggested design for clinical studies is to add marijuana, oral THC, or placebo to standard therapy under double-blind conditions: (1) Establish dose-response and dose-duration relationships for intraocular pressure

(IOP) and central nervous system effects. (2) Relate IOP and blood pressure measurements longitudinally to evaluate potential tolerance development to cardiovascular effects. (3) Evaluate central nervous system effects longitudinally for tolerance development.

World Health Organization

No recommendations made, although the report notes that, while THC has long been known to reduce the increased intraocular pressure of glaucoma, it has not been fully studied therapeutically. The report also notes that therapeutic uses of cannabinoids are being demonstrated by controlled studies in the treatment of glaucoma.

PHYSIOLOGICAL HARMS

Health Council of the Netherlands

No recommendations made.

AMA House of Delegates

No recommendations made.

British Medical Association

Further research is needed to establish the suitability of cannabinoids for immunocompromised patients, such as those undergoing cancer chemotherapy or those with HIV/AIDS.

National Institutes of Health

Risks associated with smoked marijuana must be considered not only in terms of immediate adverse effects but also long-term effects in patients with chronic diseases. The possibility that frequent and prolonged marijuana use might lead to clinically significant impairments of immune system function is great enough that relevant studies should be part of any marijuana medication development research.

Additional studies of long-term marijuana use are needed to determine if there are or are not important adverse pulmonary, central nervous system, or immune system problems.

World Health Organization

Further studies are needed on the fertility effects in cannabis users in view of the high rate of use during the early reproductive years. Further clinical and experimental research is required on the effects of cannabis on respiratory function and respiratory diseases. More studies are needed to show whether cannabis affects the risk of lung malignancies and at what level of use that may occur. In addition, more studies are needed to clarify the rather different results of pulmonary histopathological studies in animals and man.

More clinical and experimental research is needed on the effects of cannabis on immunological function. More clarity should be sought concerning the molecular mechanisms responsible for immune effects, including both cannabinoid receptor and nonreceptor events.

The possibility that chronic cannabis use has adverse effects on the cardiovascular system should have a priority in epidemiological research.

Research on chronic and residual cannabis effects is also needed. The pharmacokinetics of chronic cannabis use in humans are poorly described, and this lack of knowledge restricts the ability of researchers to relate drug concentrations in blood or other fluids and observed effects.

PSYCHOLOGICAL HARMS

Health Council of the Netherlands

No recommendations made.

AMA House of Delegates

No recommendations made.

British Medical Association

No recommendations made.

National Institutes of Health

No recommendations made.

World Health Organization

There is a need for controlled studies investigating the relationships between cannabis use, schizophrenia, and other serious mental disorders.

There is also a need for case-controlled studies comparing those experiencing cannabis problems with people who have, and do not have, alcohol and other psychoactive substance use problems.

There is a need for better delineation of the clinical features of cannabis dependence and for studies of its responsiveness to interventions aimed at assisting users to stop.

Insufficient research has been undertaken on the “amotivational” syndrome which may or may not result from heavy cannabis use. It is not clear that the syndrome exists, even though heavy cannabis use is sometimes associated with reduced motivation to succeed in school and work. New research is needed to show whether the reduced motivation seen in some cannabis users is due to other psychoactive substance use and whether it precedes cannabis use.

Further development of cognitive and psychomotor tests for controlled studies that are sensitive to the performance effects of cannabis use and that reflect the complexity of specific daily functions (e.g., driving, learning, reasoning) also need additional research.

More research is needed to examine the relationship between THC concentrations in blood and other fluids and the degree of behavioral impairment produced.

SMOKED MARIJUANA AND USE OF PLANTS AS MEDICINE

Health Council of the Netherlands

The committee believes that physicians cannot accept responsibility for a product of unknown composition that has not been subjected to quality control.

AMA House of Delegates

No specific recommendations made, but related issues are discussed in the general recommendation and drug development sections.

British Medical Association

Prescription formulations of cannabinoids or substances acting on the cannabinoid receptors should not include either cigarettes or herbal preparations with unknown concentrations of cannabinoids or other chemicals.

National Institutes of Health

Smoked marijuana should be held to standards equivalent to other

medications for efficacy and safety considerations. There might be some patient populations for whom the inhalation route might offer advantages over the currently available capsule formulation. Smoking plant material poses difficulties in standardizing testing paradigms, and components of the smoke are hazardous, especially in the immunocompromised patient. Therefore, the experts generally favored the development of alternative dosage forms, including an inhaler dosage form into which a controlled unit dose of THC could be placed and volatilized.

World Health Organization

Not discussed in the context of medical use, although many health hazards associated with chronic marijuana smoking are noted.

DRUG DEVELOPMENT

Health Council of the Netherlands

Not discussed.

AMA House of Delegates

The National Institutes of Health should use its resources to support the development of a smoke-free inhaled delivery system for marijuana or THC to reduce the health hazards associated with the combustion and inhalation of marijuana.

British Medical Association

Pharmaceutical companies should undertake basic laboratory investigations and develop novel cannabinoid analogs that may lead to new clinical uses.

National Institutes of Health

NIH should use its resources and influence to rapidly develop a smoke-free inhaled delivery system for marijuana or THC. A recommendation was made for the development of insufflation/inhalation devices or dosage forms capable of delivering purer THC or cannabinoids to the lungs free of dangerous combustion byproducts.

World Health Organization

Not discussed.

APPENDIX F

Rescheduling Criteria

DRUG ENFORCEMENT AGENCY'S FIVE-FACTOR TEST FOR RESCHEDULING*

1. The drug's chemistry must be known and reproducible.

The substance's chemistry must be scientifically established to permit it to be reproduced in dosages which can be standardized. The listing of the substance in a current edition of one of the official compendia, as defined by section 201(j) of the Food, Drug, and Cosmetic Act, 21 USC 321(f), is sufficient generally to meet this requirement.

2. There must be adequate safety studies.

There must be adequate pharmacological and toxicological studies done by all methods reasonably applicable on the basis of which it could be fairly and responsibly concluded, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, that the substance is safe for treating a specific, recognized disorder.

3. There must be adequate and well-controlled studies proving efficacy.

There must be adequate, well-controlled, well-designed, well-conducted, and well-documented studies, including clinical investigations, by experts qualified by scientific training and experience to evaluate

*Formulated in 1992 in response to a court challenge to scheduling.

the safety and effectiveness of drugs on the basis of which it could fairly and responsibly be concluded by such experts that the substance will have its intended effect in treating a specific, recognized disorder.

4. The drug must be accepted by qualified experts.

The drug must have a New Drug Application (NDA) approved by the Food and Drug Administration . . . or, a consensus of the national community of experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, accepts the safety and effectiveness of the substance for use in treating a specific, recognized disorder. A material conflict of opinion among experts precludes a finding of consensus.

5. The scientific evidence must be widely available.

In the absence of NDA approval, information concerning the chemistry, pharmacology, toxicology, and effectiveness of the substance must be reported, published, or otherwise widely available in sufficient detail to permit experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, to fairly and responsibly conclude the substance is safe and effective for use in treating a specific, recognized disorder.

SOURCES: LeCraw (1996) and 57 *Federal Register* 10499 (1992).

APPENDIX F

Rescheduling Criteria

DRUG ENFORCEMENT AGENCY'S FIVE-FACTOR TEST FOR RESCHEDULING*

1. The drug's chemistry must be known and reproducible.

The substance's chemistry must be scientifically established to permit it to be reproduced in dosages which can be standardized. The listing of the substance in a current edition of one of the official compendia, as defined by section 201(j) of the Food, Drug, and Cosmetic Act, 21 USC 321(f), is sufficient generally to meet this requirement.

2. There must be adequate safety studies.

There must be adequate pharmacological and toxicological studies done by all methods reasonably applicable on the basis of which it could be fairly and responsibly concluded, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, that the substance is safe for treating a specific, recognized disorder.

3. There must be adequate and well-controlled studies proving efficacy.

There must be adequate, well-controlled, well-designed, well-conducted, and well-documented studies, including clinical investigations, by experts qualified by scientific training and experience to evaluate

*Formulated in 1992 in response to a court challenge to scheduling.

the safety and effectiveness of drugs on the basis of which it could fairly and responsibly be concluded by such experts that the substance will have its intended effect in treating a specific, recognized disorder.

4. The drug must be accepted by qualified experts.

The drug must have a New Drug Application (NDA) approved by the Food and Drug Administration . . . or, a consensus of the national community of experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, accepts the safety and effectiveness of the substance for use in treating a specific, recognized disorder. A material conflict of opinion among experts precludes a finding of consensus.

5. The scientific evidence must be widely available.

In the absence of NDA approval, information concerning the chemistry, pharmacology, toxicology, and effectiveness of the substance must be reported, published, or otherwise widely available in sufficient detail to permit experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, to fairly and responsibly conclude the substance is safe and effective for use in treating a specific, recognized disorder.

SOURCES: LeCraw (1996) and 57 *Federal Register* 10499 (1992).

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